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Biologic Drugs for Nonasthma Indications: Clinical Evidence

Systematic Review

October 2021

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Executive Summary

Background

Chronic spontaneous urticaria (CSU) is a skin condition that causes persistent, itchy hives of unknown origin. Current treatment options are either not fully effective or have an undesirable side effect profile. Monoclonal antibodies, specifically omalizumab, have the potential to provide symptom relief to those affected.

Eosinophilic granulomatosis with polyangiitis (EGPA) is a disease characterized by eosinophilic vasculitis that affects 1 or more end-organ. The standard of care is systemic glucocorticoid steroids, which can lead to undesirable adverse events (AEs). Mepolizumab is a monoclonal antibody that targets interleukin-5 (IL-5). Mepolizumab is a promising addition or alternative to steroid therapy, because IL-5 regulates eosinophils.

Hypereosinophilic syndrome (HES) is caused by high levels of eosinophils in the blood or tissue, which can cause end-organ damage. Current therapy options, such as systemic glucocorticoid steroids, are effective but have undesirable AEs. The monoclonal antibody mepolizumab, directly affects the regulation of eosinophils, and, therefore, may prove to be as add-on or alternative therapy for this patient population.

Chronic rhinosinusitis (CRS) is a common inflammatory condition resulting in significant sino-nasal symptoms. There are 2 phenotypes of CRS differentiated by the presence or absence of nasal polyps. Long-term treatment with intranasal corticosteroids is common in individuals with CRS, and systemic corticosteroids are often used for the treatment of severe symptoms. Monoclonal antibodies including omalizumab, dupilumab, and mepolizumab decrease inflammation due to direct interaction with receptors within the inflammatory pathway and have the potential for improving symptoms and associated quality of life (QoL) measures in individuals with CRS.

The CRS phenotype chronic rhinosinusitis with nasal polyps (CRSwNP) is defined by the presence of tumor-like swellings in the nasal mucosa (i.e., nasal polyps). Long-term treatment with intranasal corticosteroids is common for the management of symptoms associated with CRSwNP. Systemic corticosteroids are utilized for the treatment of severe symptoms. Refractory cases of CRSwNP may require sino-nasal surgery and repeat surgeries for recurrent cases. Due to their anti-inflammatory effects, omalizumab, dupilumab, and mepolizumab have the potential for improving symptoms, nasal polyp size, and associated QoL measures in individuals with CRSwNP.

PICOS and Key Questions

Population

- See Table 1

Interventions

- Dupilumab (Dupixent)
- Mepolizumab (Nucala)
- Omalizumab (Xolair)

Comparators

- Another listed intervention
- Topical prescription therapies
- Standard of care
- Placebo

Effectiveness Outcomes

- Condition-specific outcomes, for example:
  - Chronic rhinosinusitis: forced expiratory volume in 1 second (FEV-1)
  - Chronic spontaneous urticaria: Urticaria Activity Score (UAS), use of other antiurticaria medications
  - Eosinophilic granulomatosis: remission rates, relapse rates
  - Hypereosinophilic syndrome: reduction in use of oral steroids
  - Nasal polyps: Nasal Polyp Score (NPS) and Nasal Congestion Score (NCS)
- Symptom control
- QoL using validated scales
- Severe exacerbations
- Hospital admissions

Harm Outcomes

- Mortality
- AEs
- Serious adverse events (SAEs)

Study Designs

- Randomized controlled trials (RCTs)

Key Questions

KQ1. What is the effectiveness of biologic drugs for chronic spontaneous urticaria, eosinophilic granulomatosis, hypereosinophilic syndrome, chronic rhinosinusitis, and nasal polyps?

KQ2. What are the harms of biologic drugs for chronic spontaneous urticaria, eosinophilic granulomatosis, hypereosinophilic syndrome, chronic rhinosinusitis, and nasal polyps?

KQ3. What are the characteristics of ongoing studies of biologic drugs to treat these conditions?

Methods

We followed standard Drug Effectiveness Review Project (DERP) methods and procedures for performing systematic reviews. We searched Ovid MEDLINE, the Cochrane Library, Google Scholar, and other evidence sources up through July 5, 2021. We identified ongoing studies through ClinialTrials.gov, the International Standard Randomized Controlled Trials Number (ISRCTN) registry, and US Food and Drug Administration resources. We selected studies for inclusion if they met our PICOS, were conducted in human participants, and were published in English. Systematic reviews were not included, but the reference lists contained in these reviews were used to identify additional studies.

We conducted a risk of bias (RoB) assessment on all eligible studies published in full-text articles. We also used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to evaluate the certainty of evidence for critical clinical outcomes reported in full-text articles. Critical clinical outcomes included weekly UAS, weekly Itch Severity Score (ISS), Dermatology Life Quality Index (DLQI), EGPA remission, EGPA relapse, oral corticosteroid dose reduction, and time to first flare occurrence for HES.

For CRS and CRSwNP, critical outcomes included NPS, NCS, Total Polyp Score (TPS), 22-item or 20-item Sino-nasal Outcome Test (SNOT-22; SNOT-20), University of Pennsylvania Smell Identification Test (UPSIT), 36-item Short Form Health Survey (SF-36), Asthma Quality of Life Questionnaire (AQLQ), 5-item or 6-item Asthma Control Questionnaire (ACQ-5; ACQ-6), Total Nasal Symptom Score (TNSS), FEV-1, and AEs.

Our full search strategy and methods are provided in Appendix A.

Key Findings

Chronic Spontaneous Urticaria

- We identified 7 *moderate* RoB RCTs and 1 *high* RoB RCT (in 10 total publications) analyzing omalizumab for the treatment of CSU.
  - Typical treatment period was 12 to 24 weeks, with 1 trial treating for 28 weeks.
  - We rated relevant outcomes as *low* to *moderate* certainty of evidence.
  - Efficacy outcomes consisted of symptom (e.g., itch, hives, angioedema) control and QoL measures.
  - Participants receiving omalizumab 300 mg achieved a statistically significant difference in the efficacy outcomes compared with the participants receiving placebo (ISS7 mean difference range, −5.8 to −3.7; UAS summed over 7 days [UAS7] mean difference range, −12.8 to −8.6; DLQI mean difference range, −4.7 to −3.1).
  - Participants receiving omalizumab 150 mg generally experienced a statistically significant difference in efficacy outcomes when compared with participants receiving placebo (ISS7 mean difference range, −3 to −2.3; UAS7 mean difference range, −6.54 to −4.89; DLQI mean difference range, −2.5 to −1.9).
  - Participants receiving omalizumab 75 mg rarely achieved a significant difference in efficacy outcomes when compared with participants receiving placebo (ISS7 mean difference from placebo, −2.96 and −0.7; UAS7 mean difference, −5.75; DLQI mean difference, −1.7).
  - Different doses of omalizumab and placebo did not significantly differ in overall AEs and SAEs.

Eosinophilic Granulomatosis With Polyangiitis

- We identified 1 *moderate* RoB RCT (in 2 publications) analyzing mepolizumab for the treatment of EGPA.
  - The trial was conducted over a 60-week period (52-week treatment period, followed by an 8-week follow up period).
  - We rated the certainty of evidence for relevant outcomes as *low* to *moderate*.
  - Efficacy outcomes consisted of the accrued time in weeks of remission and time to first relapse.

- More participants in the mepolizumab group than the placebo group achieved at least an accrued 24 weeks of remission (28% [19 of 68] vs. 3% [2 of 68], respectively; odds ratio (OR), 5.91; 95% confidence interval (CI), 2.68 to 13.03; *P* < .01).
- Time to first relapse was delayed for participants on mepolizumab compared with placebo, with a relapse occurring during trial period for 56% (38 of 68) and 82% (56 of 68) of participants respectively.
- Overall AEs showed no significant between treatment groups.
- One non-treatment-related death occurred in the mepolizumab group.

Hypereosinophilic Syndrome

- We identified 2 *moderate* RoB RCTs (in 3 publications) analyzing mepolizumab for the treatment of HES.
  - Treatment periods were between 32 to 36 weeks.
  - We rated the certainty of evidence for relevant outcomes as *low* to *moderate*.
  - Efficacy outcomes consisted of time to first flare occurrence and prednisone dose reduction.
  - Participants in the mepolizumab group had achieved statistically significant reductions in prednisone doses when compared to participants in the placebo group (84% [36 of 43] and 43% [18 of 42] respectively; hazard ratio [HR], 2.90; 95% CI, 1.59 to 5.26; *P* < .01).
  - Participants in the placebo group experienced their first flare significantly sooner than participants in the mepolizumab group (28% [15 of 54] vs. 56% [30 of 54] respectively; *P* < .01).
  - AEs either did not demonstrate statistical significance or statistical significance testing was not performed.
  - AEs that occurred more frequently in the mepolizumab group included local injection-site reactions, pain in extremities, and drug-related AEs.
  - One non-treatment-related death occurred in the mepolizumab group.

Chronic Rhinosinusitis

- We identified 11 publications analyzing biologics for the treatment of CRS: 7 RCTs, 2 subgroup analyses of RCTs, and 2 post hoc analyses of RCTs analyzing outcomes of interest.

Omalizumab

- We identified 3 RCTs for the treatment of CRS with omalizumab, with RoB ranging from *high to low*.
  - Treatment periods were between 16 weeks and 6 months.
  - Efficacy outcomes consisted of change from baseline in symptoms, and QoL.
  - More participants in the omalizumab group achieved significant symptom improvement compared with placebo (UPSIT mean difference, 3.81 to 3.86; TNSS mean difference, −1.91 to −2.09).
  - More participants in the omalizumab group achieved significant improvement in QoL when compared with placebo (SNOT-22 mean difference range, −15.04 to −16.12).
  - AEs did not vary significantly in participants in the omalizumab group compared with placebo, except in 1 study where the common cold occurred more frequently in the omalizumab group.

Dupilumab

- We identified 2 *moderate* RoB RCTs (in 6 publications) for the treatment of CRS with dupilumab.
  - Treatment periods were between 16 and 52 weeks.
  - Efficacy outcomes consisted of change from baseline in FEV-1, NPS, symptoms, and QoL.
  - More participants in the dupilumab groups achieved significant improvement in FEV-1 when compared with placebo (mean change range, 0.12 L to 0.34 L).
  - More participants in the dupilumab groups achieved significant symptom improvement when compared with placebo (UPSIT mean difference range, 7.6 to 14.8; Total Symptom Score [TSS] mean difference range, −2.8 to −4.0).
  - More participants in the dupilumab groups achieved significant improvements in QoL when compared with placebo (SNOT-22 mean difference range, −10.32 to −21.12; AQLQ mean difference, 0.57 to 0.58).
  - Common AEs included nasopharyngitis, injection-site reactions, and headache.
  - AEs did not vary significantly in the dupilumab groups compared to placebo.

Mepolizumab

- We identified 2 *moderate* RoB RCTs for the treatment of CRS with mepolizumab.
  - Treatment periods were between 48 and 52 weeks.
  - Efficacy outcomes consisted of change from baseline in symptoms.
  - More participants in the mepolizumab groups achieved significant symptom improvement compared with the placebo group.
  - More participants in the mepolizumab groups achieved significant improvement in QoL than the placebo group (SNOT-22 mean difference range, −13.2 to −16.49).
  - The most common AEs were nasopharyngitis, common cold, sinusitis, nosebleed, and headache.
  - AEs did not vary significantly in the mepolizumab groups compared to placebo.

Chronic Rhinosinusitis With Nasal Polyps

- We identified 11 publications analyzing biologics for the treatment of CRSwNP: 8 RCTs, 1 subgroup analysis of RCT, and 2 post hoc analyses of RCTs analyzing outcomes of interest.

Omalizumab

- We identified 3 RCTs for the treatment of CRS with omalizumab, 1 with a *high*, 1 with a *moderate*, and 1 with a *low* risk for bias.
  - Efficacy outcomes consisted of change from baseline in NPS and NCS.
  - More participants in the omalizumab group achieved a significant reduction in NPS compared with placebo (mean difference range, −0.59 to −1.14) and improvement of at least 1 point in NPS (56.3% [72 of 128] vs. 28.7% [15 of 129] respectively).
  - More participants in the omalizumab group achieved significant symptom improvement compared with placebo (NCS mean difference −0.5 to −0.55).
  - See above for study features impact on other symptoms and QoL and occurrence of AEs.

Dupilumab

- We identified 2 *moderate* RoB RCTs (in 5 publications) for the treatment of CRS with dupilumab.
  - See above for study features and impact on symptoms and QoL and occurrence of AEs.
  - Efficacy outcomes consisted of change from baseline in NPS and NCS.
  - More participants in the dupilumab groups achieved significant improvement in NPS when compared with placebo (mean difference range, −1.6 to −3.5).
  - More participants in the dupilumab groups achieved significant symptom improvement when compared with placebo (NCS mean difference range, −0.87 to −1.2).

Mepolizumab

- We identified 3 *moderate* RoB RCTs for the treatment of CRS with mepolizumab.
  - Treatment periods were between 25 and 52 weeks.
  - Efficacy outcomes consisted of change from baseline in TPS, need for nasal surgery, and symptoms.
  - More participants in the mepolizumab group achieved a significant reductions in TPS, need for surgery and improvement in symptoms and QoL when compared with placebo.
  - More participants in the mepolizumab groups achieved significant reduction in TPS when compared with the placebo group (treatment difference range, −0.9 to −1.3).
  - See above for impact on QoL and occurrence of AEs.

Discussion

We identified a number RCTs evaluating the use of omalizumab, dupilumab, and mepolizumab for inflammatory conditions including CSU, EGPA, HES, CRS, and CRSwNP. The certainty of evidence for efficacy and harm outcomes ranged from *low* to *moderate*. Sources of concern included imprecision and RoB (e.g., role of the funding source).

In general, the studies evaluated the efficacy of eligible interventions on surrogate markers of disease including symptoms and QoL. However, for EGPA, eligible studies examined drug impact on disease state severity through the examination of relapse rates and duration of remission. Omalizumab demonstrated efficacy in the treatment of CSU, CRS and CRSwNP in treatment periods as short as 12 weeks and up to 6 months, without significant AEs. Improvements in NPS, symptoms, and QoL measures were seen for each condition. Dupilumab was efficacious in participants with CRS and CRSwNP for improving NPS, FEV-1, symptoms, and QoL, without significant AEs. Mepolizumab demonstrated efficacy for the treatment EGPA, HES, and CRSwNP. Treatment was associated with an increase in remission time in EGPA, increase in time to first flare and decrease in steroid dose in HES, and reduction in NPS and need for surgery with concomitant improvement in symptoms and QoL in CRSwNP.

Taken together, the results of these studies demonstrate the efficacy (based on surrogate disease markers) of the biologic drugs omalizumab, dupilumab, and mepolizumab for the treatment of inflammatory conditions other than asthma and their symptoms, with a low risk for treatment-related AEs.

List of Brand Names and Generics

Table 1: Included Biologic Drugs

Generic Name	Brand Name	Manufacturer	Population of Interest	FDA Approval
Dupilumab	Dupixent	Sanofi, Regeneron, and Genzyme	Adult patients with inadequately controlled CRSwNP	March 2019
Mepolizumab	Nucala	GlaxoSmithKline	Adult patients with eosinophilic granulomatosis with polyangiitis	December 2017
			Adult and pediatric patients aged 12 years and older with HES for ≥ 6 months without an identifiable nonhematologic cause	September 2020
			Add-on maintenance treatment for adults with CRSwNP and an inadequate response to intranasal corticosteroids	July 2021
Omalizumab	Xolair	Genetech and Novartis	Individuals aged 12 years and older with CSU who remain symptomatic despite H1-antihistamine treatment	March 2014
			Adults with nasal polyps with an inadequate response to nasal corticosteroids	November 2020

Abbreviations. CRSwNP: chronic rhinosinusitis with nasal polyps; CSU: chronic spontaneous urticaria; FDA: US Food and Drug Administration; HES: hypereosinophilic syndrome.

Background

Chronic spontaneous urticaria (CSU), additionally known as chronic idiopathic urticaria, is a skin condition with the appearance of unexplained itchy hives that last for at least 6 weeks and is caused by histamine release.[1] This disease state is known to affect patient's emotional and physical health.[2] Current standard treatment has been H_1-antihistamines, but even with the use of higher doses than approved by the US Food and Drug Administration (FDA), a majority of patients are not relieved of their symptoms.[3] Second-line treatment options, such as systemic glucocorticoids, dapsone, and methotrexate are associated with undesirable side effects.[3] Omalizumab, a monoclonal antibody approved for moderate-to-severe persistent allergic asthma, has a high-affinity receptor for the fragment crystallizable region of immunoglobulin E (IgE).[4] IgE is known to activate mast cells, which are associated with histamine release, and subsequently, can cause urticaria.[4] Omalizumab's mechanism of action makes it a potentially useful agent in the treatment of this patient population.

Eosinophilic granulomatosis with polyangiitis (EGPA), formally known as Churg-Strauss syndrome, is an eosinophilic disease that can affect 1 or more end-organ.[5] Eosinophils may also cause accompanying neuropathy, sinusitis, pulmonary infiltrates, or asthma.[5] Systemic glucocorticoid steroid therapy is the current basis of treatment in this patient population, but

although they are initially effective, many patients experience relapse or unfavorable adverse events (AEs).[5] Mepolizumab is an anti-interleukin-5 (anti-IL-5) monoclonal antibody.[5] The binding of mepolizumab to IL-5 blocks the receptor on the eosinophil to prevent proliferation, maturation, and differentiation of the cell.[5]

Hypereosinophilic syndrome (HES) is characterized by high levels of eosinophils in the blood or tissues, typically treated with glucocorticoids or immunosuppressive therapy.[6] The goal of treatment is to reduce the risk of end-organ damage.[6] Though the pharmacotherapy options are effective, adverse side effects make them less desirable.[7] As with its use for EGPA, the effectiveness of mepolizumab comes from its binding to IL-5, blocking the receptors on the eosinophils.[5]

Chronic rhinosinusitis (CRS) is a common condition defined by sino-nasal symptoms including nasal obstruction, rhinorrhea, and loss of sense of smell, resulting in facial pain, impaired sleeping patterns, and diminished quality of life (QoL).[8] Individuals with CRS often have comorbid asthma, which places them at higher risk for severe and refractory disease.[8] There are 2 phenotypes of CRS based on the presence or absence of nasal polyps.[8] CRS with nasal polyps (CRSwNP) differs from CRS without nasal polyps based on the presence of tumor-like swellings in the nasal mucosa (i.e., nasal polyps).[8] Diagnosis for CRSwNP occurs through direct or endoscopic visualization of polyps within the nasal cavity.[8] Long-term treatment is common in individuals with CRS, including the mainstay of therapy, intranasal corticosteroids.[9] In cases of CRS exacerbation, systemic corticosteroids are utilized to control symptoms.[8] In individuals with severe CRSwNP refractory to intranasal steroid therapy, surgery is often required.[8] Nasal polyp recurrence is possible, resulting in the need for multiple surgeries.[9] CRS is characterized by inflammation associated with inflammatory cytokines including (interleukins) IL-4, IL-5, and IL-13, and the local presence of eosinophils, basophils, and mast cells.[10] Monoclonal antibodies including omalizumab, dupilumab, and mepolizumab decrease inflammation due to direct interaction with receptors within the inflammatory pathway, and have the potential for improving symptoms and associated QoL measures in individuals with CRS.[8] The anti-IgE and anti-IL-5 properties of omalizumab and mepolizumab, respectively, make them attractive candidates for the treatment of severe and refractory CRS. Dupilumab is an anti-IL-4 monoclonal antibody that inhibits IL-4 signaling and the downstream activation of type 2 helper T-cell-mediated inflammation.[11] Dupilumab has demonstrated efficacy in the treatment of asthma and atopic dermatitis and sino-nasal symptoms in individuals with asthma,[11] making it a viable option for the treatment of CRSwNP. Dupilumab received FDA approval as add-on maintenance treatment for adults with uncontrolled CRSwNP in June 2019. Omalizumab received FDA approval for this indication in August 2020, and mepolizumab followed with FDA approval in July 2021.

The Drug Effectiveness Review Project (DERP) had previously commissioned a systematic review on biological drugs to treat asthma, and they had additional interest in expanding this work to include other approved indications in a separate review, which follows here.[12]

PICOS

Population

- See Table 1, *Population of Interest*

Interventions

- Dupilumab (Dupixent)
- Mepolizumab (Nucala)
- Omalizumab (Xolair)

Comparators

- Another listed intervention
- Topical prescription therapies
- Standard of care
- Placebo

Effectiveness Outcomes

- Condition-specific outcomes, for example:
  - Chronic spontaneous urticaria: Urticaria Activity Score (UAS) or use of other antiurticaria medications
  - Eosinophilic granulomatosis with polyangiitis: remission and relapse rates
  - Hypereosinophilic syndrome: reduction in use of oral steroids
  - Chronic rhinosinusitis: forced expiratory volume in 1 second (FEV-1)
  - Chronic rhinosinusitis with nasal polyps: Nasal Polyp Score (NPS) and Nasal Congestion Score (NCS)
- Symptom control
- QoL (using validated scales)
- Severe exacerbations
- Hospital admissions

Harm Outcomes

- Mortality
- AEs
- Serious adverse events (SAEs)

Study Designs

- Randomized controlled trials (RCTs)

Key Questions

KQ1. What is the effectiveness of biologic drugs for chronic spontaneous urticaria, eosinophilic granulomatosis, hypereosinophilic syndrome, and chronic rhinosinusitis, nasal polyps?

KQ2. What are the harms of biologic drugs for chronic spontaneous urticaria, eosinophilic granulomatosis, hypereosinophilic syndrome, chronic rhinosinusitis, and nasal polyps?

KQ3. What are the characteristics of ongoing studies of biologic drugs to treat these conditions?

Methods

We followed standard DERP methods and procedures for performing systematic reviews. We searched Ovid MEDLINE, the Cochrane Library, Google Scholar, and other evidence sources up through July 5, 2021. We identified ongoing studies through ClinialTrials.gov, the International Standard Randomized Controlled Trials Number (ISRCTN) registry, and FDA resources. We selected studies for inclusion if they met our PICOS, were conducted in human participants, and were published in English. Systematic reviews were not included, but the reference lists contained in these reviews were used to identify additional studies.

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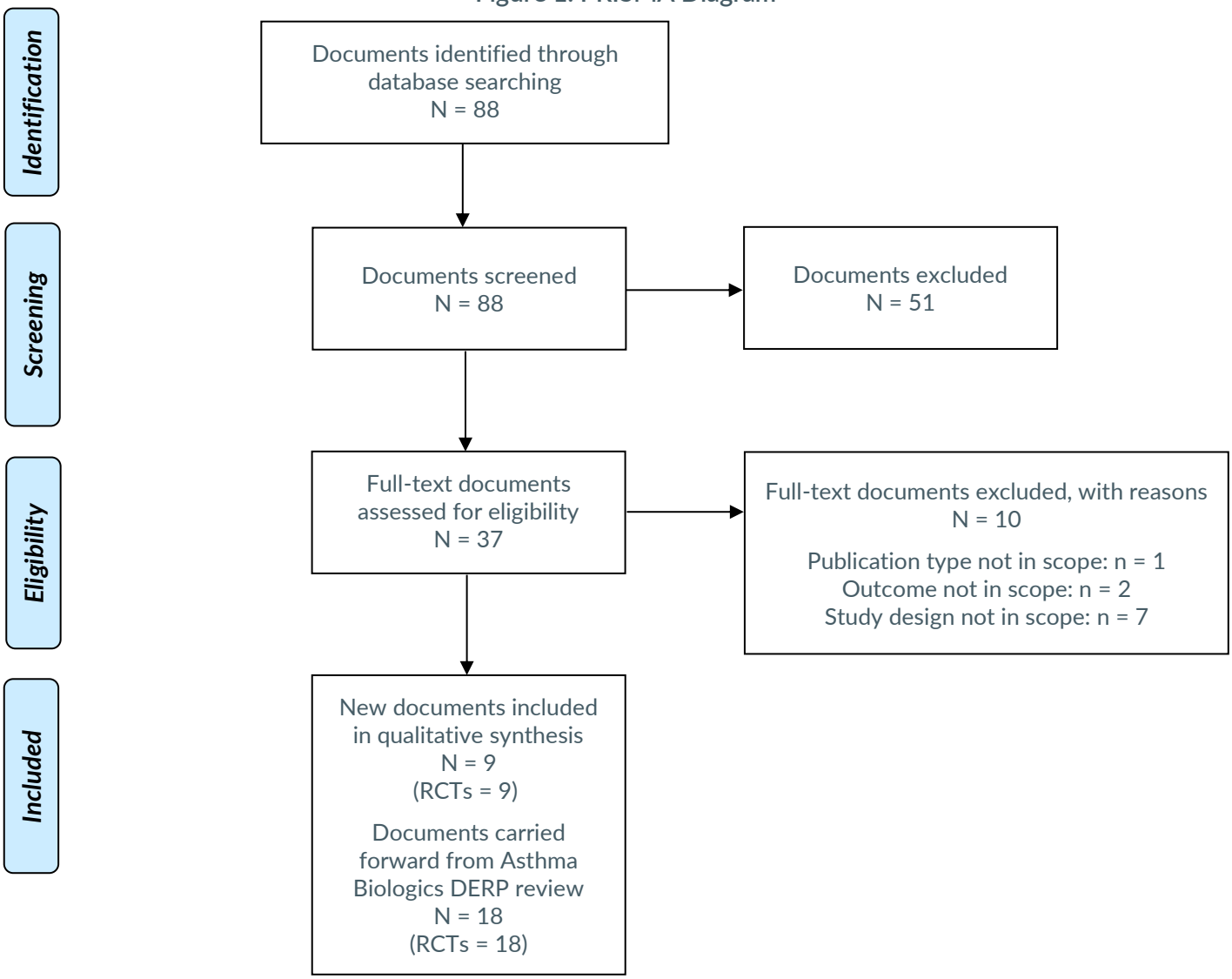
For CRS and CRSwNP, critical outcomes included Nasal Polyp Score (NPS), Nasal Congestion Score (NCS), Total Polyp Score (TPS), 22-item or 20-item Sino-nasal Outcome Test (SNOT-22; SNOT-20), University of Pennsylvania Smell Identification Test (UPSIT), 36-item Short Form Health Survey (SF-36), Asthma Quality of Life Questionnaire (AQLQ), 5-item or 6-item Asthma Control Questionnaire (ACQ-5; ACQ-6), Total Nasal Symptom Score (TNSS), forced expiratory volume in one second (FEV-1), and adverse effects (AEs) (see Table 10).

Our full search strategy and methods are provided in Appendix A.

Findings

Figure 1 shows the literature flow through the review and associated PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) characteristics.

Figure 1. PRISMA Diagram



Abbreviations. DERP: Drug Evidence Review Project; RCT: randomized controlled trial.

Chronic Spontaneous Urticaria

Study Characteristics

We identified 10 publications analyzing omalizumab for the treatment of CSU: 8 RCTs with 1 additional report of study data and 1 subgroup analysis.[1-4,13-18] These studies evaluated the use of omalizumab compared with placebo in participants with moderate to severe CSU.[1-4,13-18] Participant sample size ranged from 39 to 336, with follow-up between 20 to 60 weeks.[1-4,13-18] All of the studies used a 300 mg dosage of omalizumab in the treatment group versus placebo; some of the trials also compared varying doses of omalizumab ranging from 75 mg to 375 mg (with the majority set at 75 mg, 150 mg, and 300 mg) versus placebo. [1-4,13-18]

Table 2. Description of Assessments and Questionnaires for CSU

Measure	Abbreviation	Meaning	Scoring
Urticaria Activity Score[4]	UAS	Higher score indicates more activity	0 to 6
Weekly Urticaria Activity Score[13]	UAS7	Higher score indicates more activity	0 to 42
Weekly Itch Severity Score[2]	ISS7	Higher score indicates more severity	0 to 21
Dermatology Life Quality Index[4]	DLQI	Lower score indicates better QoL	0 to 30
Chronic Urticaria Quality of Life[3]	CU-Q_2oL	Lower score indicates better QoL	0 to 100
Angioedema Activity Score[3]	AAS	Higher score indicates more activity	0 to 105
Angioedema Quality of Life[3]	AE-QoL	Lower score indicates better QoL	0 to 100
Skindex-29[15]	–	Lower score indicates better QoL	0 to 100

Abbreviations. CSU: chronic spontaneous urticaria; QoL: quality of life.

Efficacy outcomes consisted of several QoL measures including DLQI, Chronic Urticaria Quality of Life (CU-Q_2oL), Angioedema Quality of Life (AE-QoL), and Skindex-29, which are summarized in Table 2.[1-4,13-18] Further, the activity and severity of urticaria, itch, angioedema, and number and size of hives present were evaluated.[1-4,13-18]

A majority of the trials enrolled participants between the ages of 12 to 75 years, a UAS summed over 7 days (UAS7) of 16 or greater, an ISS over 7 days (ISS7) of 8 or greater, and a diagnosis of uncontrolled chronic urticaria, with no known underlying cause for 6 months or longer, despite the use of up to 4 times the approved doses of H_1-antihistamine.[1,2,4,16-18] Moreover, participants could not be taking immunosuppressant therapy (e.g., oral or parenteral corticosteroids, methotrexate, cyclosporine) for at least 4 weeks prior to screening.[1-4,13-15,18]

Overall, harm outcomes were assessed based on severity and relation to treatment.[1-4,13-18] For this evaluation, 7 RCTs were rated as having a *moderate* RoB due to funding sources and lack of information on outcome assessors blinding, and 1 RCT with a *high* RoB due to baseline imbalances, and lack of intention-to-treat analysis, allocation concealment, and information on randomization. Table 3 provides a characteristic overview of the included studies for this disease state. Complete trial descriptions are provided in Appendix B.

Table 3. Study Characteristics for CSU

Author, Year Registration Number, Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Maurer et al., 2011[13] Moderate	N = 49	Omalizumab (75 to 375 mg) SQ every 2 to 4 weeks based on weight and total serum IgE at screening, n = 27 Placebo SQ every 2 to 4 weeks, n = 22	Randomized, double-blind, placebo-controlled, parallel-group	27 weeks (3-week screening period and 24-week treatment period)
Maurer et al., 2013[2] NCT01292473 ASTERIA II Moderate	N = 323	Omalizumab SQ every 4 weeks • 75 mg, n = 82 • 150 mg, n =83 • 300 mg, n = 79 Placebo SQ every 4 weeks, n = 79	International, multicenter, randomized, double-blind, placebo-controlled	28 weeks (12-week treatment period and a 16-week follow up)
Kaplan et al., 2013[4] NCT01264939 GLACIAL Moderate	N = 336	Omalizumab 300 mg SQ every 4 weeks, n = 252 Placebo SQ every 4 weeks, n = 84	Global phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group	40 weeks (24-week treatment and a 16-week follow up)
Saini et al., 2015[1] NCT01287117 ASTERIA I Moderate	N = 319	Omalizumab SQ every 4 weeks • 300 mg, n = 81 • 150 mg, n = 80 • 75 mg, n = 78 Placebo SQ every 4 weeks, n = 80	Randomized, double-blind, placebo-controlled	40 weeks (24-week treatment and a 16-week follow up)
Staubach et al., 2016[3] Staubach et al., 2018[14] NCT01723072 X-ACT Moderate	N = 91	Omalizumab (150 mg × 2) SQ every 4 weeks, n = 44 Placebo SQ every 4 weeks, n = 47	Multicenter, randomized, double-blind, placebo-controlled,	36 weeks (28-week treatment and 8-week follow-up)
Metz et al., 2017[15] NCT01599637 Moderate	N = 30	Omalizumab 300 mg SQ every 4 weeks, n = 20 Placebo SQ every 4 weeks, n =10	Exploratory, phase 2, randomized, double-blind, placebo-controlled, parallel group	20 weeks (12-week treatment and an 8-week follow up)
Hide et al., 2017[16] NCT02329223 POLARIS	N = 218	Omalizumab SQ every 4 weeks • 150 mg, n = 71 • 300 mg, n = 73	Phase 3, multicenter randomized, double-blind,	26 weeks (2-week screening, 12-week treatment,

Author, Year Registration Number, Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Moderate		Placebo SQ every 4 weeks, n = 74	placebo-controlled, parallel-group	12-week follow up
Hide et al., 2018[17] NCT02329223 POLARIS Moderate	N = 105	Omalizumab SQ every 4 weeks • 150 mg, n = 34 • 300 mg, n = 35 Placebo SQ every 4 weeks, n = 36	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group: subgroup analysis	26 weeks (2-week screening, 12-week treatment, 12-week follow up
Casale et al., 2019[18] NCT02392624 XTEND-CIU High	N = 134	Omalizumab 300 mg SQ every 4 weeks, n = 81 Placebo SQ every 4 weeks, n = 53	Multicenter, randomized, double-blind, placebo-controlled	60 weeks (24-week open label, 24-week double-blind treatment, and 12-week follow up)

Abbreviations. CSU: chronic spontaneous urticaria; IgE: Immunoglobulin E; SQ: subcutaneous.

Efficacy Outcomes

Table 4 provides a summary of the GRADE ratings for biologics in CSU. Overall, we rated relevant outcomes as *low* to *moderate* certainty of evidence. In general, the studies demonstrated efficacy benefits of omalizumab when compared with placebo in the treatment of CSU.

Table 4. Summary of Findings (GRADE) for CSU

Outcome Studies Sample Size	Certainty of Evidence Treatment Groups	Relationship	Rationale
Change in UAS7 from baseline 7 RCTs[1-4,13,15,16,18] N = 1,500	Moderate Omalizumab vs. placebo	Omalizumab was superior to placebo	Downgraded 1 level for risk of bias
Change in ISS7 from baseline 4 RCTs[1,2,4,16] N = 860	Moderate Omalizumab vs. placebo	Omalizumab was superior to placebo	Downgraded 1 level for risk of bias
Change in DLQI from baseline 7 RCTs[2-4,15,16,18] N = 1,132	Moderate Omalizumab vs. placebo	Omalizumab was superior to placebo	Downgraded 1 level for risk of bias
AEs	Low	Statistical testing not performed for AEs between study groups.	Downgraded 1 level for risk of

Outcome Studies Sample Size	Certainty of Evidence Treatment Groups	Relationship	Rationale
7 RCTs[1-4,13,15,16,18] N = 1,366	Omalizumab vs. placebo	Results suggest generally similar occurrence of AEs between omalizumab and placebo	bias and 1 level for indirectness

Abbreviations. AE: adverse event; CSU: chronic spontaneous urticaria; DLQI: Dermatology Life Quality Index; GRADE: Grading of Recommendation, Assessment, Development, and Evaluation approach; ISS7: Itch Severity Score over 7 days; RCT: randomized controlled trial; UAS7: Urticaria Activity Score summed over 7 days.

At 24 weeks, Maurer and colleagues found that participants who received omalizumab had significantly greater reduction in UAS7 scores than those who received placebo (−17.8 vs. −7.9; mean difference, 9.9; 95% confidence interval [CI], 2.7 to 17.1; *P* < .01).[13] Secondary outcomes found statistical significance for omalizumab over placebo for both areas under the curve of UAS over the 24 weeks (*P* < .01) and wheal score reduction (mean, −9.2 vs. −3.3; *P* < .01).[13] Other secondary outcomes demonstrated greater protection for CSU symptoms for participants in omalizumab group compared with participants in placebo group (see Appendix B).[13]

Both ASTERIA II and ASTERIA I reported significance differences for the primary outcome of change in ISS7 for participants in the omalizumab 150 mg group (ASTERIA II: mean change, −8.1; *P* < .01; ASTERIA I: mean change, −6.7; *P* < .01) and omalizumab 300 mg group (ASTERIA II: mean change, −10.5; *P* < .01; ASTERIA I: mean change, −9.4; *P* < .01) when compared with participants in placebo group (ASTERIA II: mean change, −5.1; ASTERIA I: mean change, −3.6).[1,2] Additionally, authors of the ASTERIA I study reported statistical significance with the primary outcome of change in ISS7 for omalizumab 75 mg (mean change, −6.5; *P* < .01), where ASTERIA II found no difference.[1,2] Of note, ASTERIA II demonstrated superiority for change in DLQI score of omalizumab 150 mg (mean change, −8.3; *P* = .02) and 300 mg (mean change, −10.2; *P* < .01) when compared with placebo (mean change; −6.1), while ASTERIA I showed significance with omalizumab 300 mg (mean change, −10.3; *P* < 0.1) compared with placebo (mean change, −6.13).[1,2] Other secondary outcomes found similar trends as the primary outcome regarding significance (See Appendix B). [1,2]

Kaplan and colleagues reported a significant change in ISS7 for participants in the omalizumab 300 mg group versus the placebo (−8.6 and −4.0, respectively; mean difference, −4.5; 95% CI, −6.0 to −3.1; *P* < .01).[4] The change in UAS7 found a mean change of −19.0 in omalizumab 300 mg group versus −8.5 in the placebo group (mean difference, −10.0; 95% CI, −13.2 to −6.9; *P* < .01).[4] Similar to the ASTERIA trials, the mean change in DLQI score also demonstrated significant improvement in the omalizumab group (mean change, −9.7; *P* < .01) when compared with the placebo group (mean change, −5.1).[4] Other secondary outcomes found similar trends as the primary outcome, with all efficacy end points demonstrating statistical significance with omalizumab when compared with placebo (See Appendix B).[4]

Staubach and colleagues observed a mean change in CU-Q_2oL of −23.9 for the omalizumab group (*P* < .01) and −14.7 for the placebo group.[3,14] Omalizumab performed significantly better when compared with a placebo in reduction of AE-QoL (−41.4 vs. −24.2), DLQI score (−10.5 vs. −5.6), and UAS7 (−16.8 vs. −6.5).[3,14] During the 28-week treatment period, the omalizumab

group experienced an average of 14.6 angioedema-burdened days, while the placebo group averaged 49.5 days.[3,14]

Metz and colleagues evaluated the efficacy outcomes of 17 participants in the omalizumab group and 8 participants in the placebo group.[15] Omalizumab demonstrated a greater reduction in the itch component (−11.4 vs. −3.8 respectively; *P* = .01) and hives component (−11.6 vs. −3.8 respectively; *P* = .02) of the UAS7 versus placebo.[15] Global assessments of symptoms from participants (0.9 vs. 1.9 respectively; *P* = .03) and investigators (0.8 vs. 2.0 respectively; *P* = .02) was also found to be superior in the omalizumab group over placebo.[15] Similar to ASTERIA I, ASTERIA II, and the study by Staubach and colleagues, QoL assessments used in this study (DLQI, CU-Q_2oL) both obtained significance (*P* < .01) for participants on omalizumab compared with placebo (Appendix B). [1-3,14,15]

Hide and colleagues reported statistical significance (*P* < .01) in their primary outcome of change in ISS7 compared with placebo, with increased omalizumab doses achieving a greater mean difference from baseline (omalizumab 300 mg: −10.22; omalizumab 150 mg: −8.80; placebo: −6.5).[16] Change in UAS7 (omalizumab 300 mg: −22.4; *P* < .01; omalizumab 150 mg: −18.79; *P* < .01) achieved statistical significance compared to placebo, with a greater benefit seen with higher doses, though statistical testing was not conducted between the 2 doses. Similar results were demonstrated with change in DLQI (−8.4; *P* < .01 vs. −7.29; *P* =.01).[16] Other efficacy outcomes and the subgroup analysis of the Japanese participants produced comparable results to the parent POLARIS trial (Appendix B).[17]

Casale and colleagues published the results from the XTEND-CIU trial.[18] At the end of the double-blind phase, DLQI did not worsen for 66% of participants in the omalizumab group and for 19.8% of participants in placebo group (numerator and denominator data were not reported; *P* < .01).[18] Percentage of participants experiencing clinical worsening also occurred less for those in the omalizumab group compared with the placebo group (21% vs. 60.4%; *P* < .01).[18]

Harm Outcomes

The included trials did not perform statistical testing for AEs between study groups.[1-4,13-18] The harm outcomes between participants in the omalizumab group and participants in the placebo group were generally similar, though each trial reported varying common AEs.[1-4,13-18] The most consistently reported common AE in each group was nasopharyngitis, although there were mixed results for prevalence in each group.[4,13,15,16] Maurer and colleagues reported lower rates of nasopharyngitis for omalizumab participants than for the placebo participants (33.3% [9 of 27] vs. 50% [11 of 22]); Hide and colleagues reported a higher frequency for omalizumab participants (omalizumab 300 mg: 4.1%, omalizumab 150 mg: 4.2%, placebo: 0%), and Kaplan and colleagues found comparable results in each group (8.7% vs. 8.4% respectively). [4,13,16] Two RCTs reported a higher incidence of headache for omalizumab group participants compared with placebo.[4,13]

When evaluating the included studies overall, discontinuation due to an AE occurred in 12 omalizumab participants (3 in omalizumab 75 mg, 5 in omalizumab 150 mg, and 4 in omalizumab 300 mg) and in 6 placebo participants.[1-3,13,14,16,17] No deaths occurred in any of the included studies pertaining to this topic.[1-4,13-18] Refer to Appendix B, Table B3 for comprehensive list of harm outcomes.

Eosinophilic Granulomatosis With Polyangiitis

Study Characteristics

We identified 2 publications analyzing mepolizumab for the treatment of EGPA: 1 RCT and 1 post hoc analysis of the RCT.[5,19] A total of 136 participants underwent randomization in a 1:1 ratio to receive either omalizumab or placebo.[5] Enrolled participants were 18 years and older with a diagnosis of relapsing or refractory EGPA for at least 6 months.[5] Efficacy outcomes consisted of disease remission results (defined as a Birmingham Vasculitis Activity Score [BVAS] of 0 and prednisone/prednisolone dose ≤ 4 mg daily), relapse results (defined as BVAS > 0, active asthma symptoms, worsening Asthma Control Questionnaire [ACQ; Table 5], active nasal or sinus disease), and steroid use.[5] The post hoc analysis examined participants experiencing any clinical benefit during the treatment study, defined as a composite outcome of the previously mentioned efficacy endpoints.[19] A summary of the assessments are provided in Table 5.

Table 5. Description of Assessment and Questionnaires for EGPA

Measure	Abbreviation	Meaning	Scoring
Birmingham Vasculitis Activity Score[5]	BVAS	Higher score indicates more disease activity	0 to 63
Asthma Control Questionnaire[5]	ACQ	Higher score indicates less disease control	0 to 6

Abbreviation. EGPA: eosinophilic granulomatosis with polyangiitis.

Participants were required to be on a stable dose of prednisone or prednisolone (≥ 7.5 mg to ≤ 50 mg) and could be on immunosuppressive therapy.[5] Those with life-threatening or organ-threatening EGPA were excluded from participation.[5] Overall, harm outcomes were assessed based on severity and relation to treatment.[5] We determined the RCT to have a *moderate* RoB due to funding source and differences in baseline immunosuppressive therapy. Table 6 provides a characteristic overview of the included study for this disease state, and Appendix B provides complete study information.

Table 6. Study Characteristics for EGPA

Author, Year Registration Number, Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Wechsler et al., 2017[5] NCT02020889 Moderate	N = 136	Mepolizumab 300 mg SQ every 4 weeks, n = 68 Placebo SQ every 4 weeks, n = 68	Phase 3, randomized, placebo-controlled, double-blind, parallel-group,	60 weeks (52-week treatment period; 8-week follow up period)
Steinfeld et al., 2019[19] NCT02020889	N = 136	Mepolizumab 300 mg SQ every 4 weeks, n = 68 Placebo SQ every 4 weeks, n = 68	Phase 3, randomized, placebo-controlled, double-blind, parallel-group: post hoc analysis	60 weeks (52-week treatment period; 8-week follow up period)

Abbreviations. EGPA: eosinophilic granulomatosis with polyangiitis; SQ: subcutaneous.

Efficacy Outcomes

We rated the certainty of evidence for relevant outcomes as *low* to *moderate*. We downgraded the evidence for imprecision, RoB, or both (Table 7).

Table 7. Summary of Findings (GRADE) for EPGA

Outcome Studies Sample Size	Certainty of Evidence Treatment Groups	Relationship	Rationale
Remission[a] 1 RCT[5] N = 136	Low Mepolizumab vs. placebo	Mepolizumab increased accrued time in remission compared to placebo	Downgraded 1 level for imprecision and 1 level for risk of bias
Relapse[b] 1 RCT[5] N = 136	Low Mepolizumab vs. placebo	Mepolizumab delayed occurrence of first relapse compared to placebo	Downgraded 1 level for imprecision and 1 level for risk of bias
AEs 1 RCT[5] N = 136	Moderate Mepolizumab vs. placebo	There was no statistical difference in AEs between mepolizumab and placebo	Downgraded 1 level for imprecision

Notes. [a] Total remission defined as BVAS = 0 and a prednisone/prednisolone dose of ≤ 4 mg daily over treatment period. [b] Relapse defined as BVAS > 0, active asthma symptoms, worsening ACQ (version 6), active nasal disease, or active sinus disease.
Abbreviations. ACQ: Asthma Control Questionnaire; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; GRADE: Grading of Recommendation, Assessment, Development, and Evaluation approach; RCT: randomized controlled trial.

Wechsler and colleagues reported the 2 primary end points were met.[5] The primary categorical outcome of total accrued weeks in remission over the treatment period showed statistical significance for remission of 24 weeks or more.[5] This portion of the endpoint was achieved in 28% (19 of 68) of the mepolizumab group and 3% (2 of 68) of the placebo group (odds ratio [OR], 5.91; 95% CI, 2.68 to 13.03; $P < .01$).[5] The second primary outcome of remission at week 36 and week 48 was significant for the mepolizumab group when compared to placebo (32% [22 of 68] vs. 3% [2 of 68] respectively; OR, 16.74; 95% CI, 3.61 to 77.56; $P < .01$).[5] The time-to-event of EGPA relapse before completion of trial period occurred in 82% (56 of 68) of the participants in the placebo group and 56% (38 of 68) in participants in the mepolizumab group.[5] Refer to Appendix B for complete outcome results. Steinfeld and colleagues found any clinical benefit (defined as the composite of the efficacy outcomes in the publication by Wechsler et al.) to occur more for participants in the mepolizumab group when compared with participants in the placebo group (ranging from 78% to 87% and 32% to 53%, respectively).[19]

Harm Outcomes

Wechsler and colleagues reported no significant differences between treatment groups regarding AEs.[5] A comparable occurrence of overall AEs were reported in the mepolizumab group (97% [66 of 68]) compared with the placebo group (94% [64 of 68]).[5] There were more AEs considered to be treatment-related in the mepolizumab group compared with placebo (51% [35 of 68] vs. 35% [24 of 68], respectively).[5] SAEs were reported less in the mepolizumab group

compared with placebo (18% [12 of 68] vs. 26% [18 of 68], respectively).[5] Of the reported SAEs, only 4% (3 of 68) in each treatment group were considered treatment-related.[5] Discontinuation due to AEs occurred in 3% (2 of 68) of the mepolizumab group versus 1% (1 of 68) in the placebo group.[5] No deaths occurred in the placebo group, and though 1 death occurred in the mepolizumab group (cardiac arrest), it was not attributed to the study drug.[5]

Hypereosinophilic Syndrome

Study Characteristics

We identified 3 publications analyzing mepolizumab for the treatment of HES; 2 RCTs and 1 subgroup analysis of the RCT.[6,7,20] The included studies evaluated the use of mepolizumab compared with placebo in participants with HES.[6,7,20] Participant sample size ranged from 13 to 108, with a follow up of 32 to 36 weeks.[6,7,20] One RCT included participants 18 to 85 years old diagnosed with HES (≥ 6 months prior to randomization) who were also identified as having eosinophilia-related organ involvement.[6] The subgroup analysis of the RCT further evaluated participants with lymphocytic variant HES.[20] The phase 3 RCT enrolled participants aged 12 years or older who had uncontrolled HES and were receiving stable background HES therapy (≥ 4 weeks prior to randomization).[7] Efficacy outcomes for 1 RCT consisted of time to first flare occurrence, while the other RCT focused primarily on prednisone dose reduction.[6,7] Harm outcomes included the number and percentage of participants experiencing AEs.[6,7] All trials ensured participants were negative for FIPI-like-1-platelet-derived-growth-factor-receptor-α-fusion-gene HES prior to randomization, since treatment with imatinib is first-line therapy for that patient population.[6,7,20] Both RCTs have a *moderate* RoB due to funding source and author disclosure of interests.[6,7] Table 8 provides a characteristic overview of the included studies for HES. Refer to Appendix B, Table B3 for complete trial descriptions.

Table 8. Study Characteristics for HES

Author, Year Registration Number, Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Rothenberg et al., 2008[6] NCT00086658 Moderate	N = 85	Mepolizumab 750 mg infused every 4 weeks, n = 43 Placebo infused every 4 weeks, n = 42	International, randomized, double-blind, placebo-controlled	36 weeks
Roufosse et al., 2010[20] NCT00086658	N = 13	Mepolizumab 750 mg infused every 4 weeks, n = 7 Placebo infused every 4 weeks, n = 6	International, randomized, double-blind, placebo-controlled	36 weeks
Roufosse et al., 2020[7] NCT02836496 Moderate	N = 108	Mepolizumab 300 mg SQ every 4 weeks, n = 54 Placebo SQ every 4 weeks, n = 54	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group	32 weeks

Abbreviations. HES: hypereosinophilic syndrome; SQ: subcutaneous.

Efficacy Outcomes

We rated the certainty of evidence for relevant outcomes as *low* to *moderate* (Table 9). Overall, eligible studies demonstrated efficacy benefits of mepolizumab when compared with placebo in the treatment of HES.

Table 9. Summary of Findings (GRADE) for HES

Outcome Studies Sample Size	Certainty of Evidence Treatment Groups	Relationship	Rationale
Oral corticosteroid dose reduction 1 RCT[6] N = 85	Moderate Mepolizumab vs. placebo	Mepolizumab significantly reduced the use of prednisone dose during treatment when compared to placebo	Downgraded 1 level for imprecision
Time to first flare occurrence 1 RCT[7] N = 108	Moderate Mepolizumab vs. placebo	Mepolizumab occurrence of flares was 50% lower than with placebo	Downgraded 1 level for imprecision
AEs 2 RCTs[6,7] N = 193	Low Mepolizumab vs. placebo	Statistical analysis was not performed on treatment-related AEs. Generally, AE occurrence was similar between the treatment groups.	Downgraded 1 level for risk of bias and 1 level for indirectness

Abbreviations. AE: adverse event. GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; HES: hypereosinophilic syndrome; RCT: randomized controlled trial.

Rothenberg and colleagues reported the primary end point of prednisone doses of ≤ 10 mg daily for ≥ 8 consecutive weeks was achieved by 84% (36 of 43) in the mepolizumab group and 43% (18 of 42) in placebo group (hazard ratio [HR], 2.90; 95% CI, 1.59 to 5.26; $P < .01$).[6] A greater benefit was observed in participants on mepolizumab when they were receiving at least prednisone 30 mg daily at baseline, when compared to ≤ 30 mg daily.[6] All secondary and exploratory endpoints, excluding 12-item Short Form Health Survey (SF-12) summary score, were statistically significant with a $P < .01$ for each (see Appendix B, Table B2).[6] The subgroup analysis also demonstrated similar results for participants with lymphocytic variant HES.[20]

Roufosse and colleagues reported the primary endpoint (portion of participants who experienced 1 or more predefined flare during the study) occurred 50% less in the mepolizumab group when compared with placebo (28% [15 of 54] vs. 56% [30 of 54]; $P < .01$).[7] The mepolizumab group had a 66% lower risk of their first flare taking place during the treatment period.[7] From weeks 20 to 32, significantly fewer participants receiving mepolizumab experienced a flare or withdrew from the study compared with placebo.[7] Mepolizumab was also shown to improve fatigue severity over placebo (median change, −0.66 vs. 0.32; $P = .04$).[7] Refer to Appendix B, Table B2 for comprehensive primary and secondary outcome results.

Harm Outcomes

Rothenberg and colleagues and Roufosse and colleagues did not perform statistical significance testing for treatment-related AEs between mepolizumab group participants and placebo group participants.[6] Each study experienced 1 death, both in the mepolizumab group, neither of which were treatment-related.[6] Rothenberg and colleagues found participants in the mepolizumab group experienced greater overall treatment-related AEs when compared with participants in the placebo group (37% [16 of 43] vs. 29% [12 of 42]), including arthralgia (9% [4 of 43] vs. 5% [2 of 42]) and fatigue (9% [4 of 43] vs. 2% [1 of 42]).[6] Similarly, Roufosse and colleagues demonstrated a higher incidence of treatment-related AEs in the mepolizumab group versus placebo group (22% [12 of 54] vs. 13% [7 of 54]).[6] Refer to Appendix B, Table B3 for harm outcomes.

Chronic Rhinosinusitis and Chronic Rhinosinusitis With Nasal Polyps

Evidence Summary

We found 12 RCTs that met our criteria for the listed interventions. Of these 12 studies, 3 evaluated the use of omalizumab, 6 evaluated dupilumab, and 3 evaluated mepolizumab.[9-11,21-29] Ten of the 12 studies included only participants with CRSwNP. When combining the evidence, we rated relevant outcomes as *low* to *moderate* for omalizumab, *low* to *moderate* for dupilumab, and *moderate* for mepolizumab. Outcomes of interest for this review included FEV-1, NPS, NCS, symptom control, QoL, AEs, and SAEs. Impact on FEV-1 has not been reported for participants receiving omalizumab or mepolizumab therapy. Impact on NCS has not been reported for participants receiving mepolizumab therapy.

Table 10. Description of Assessments and Questionnaires for CRS and CRSwNP

Measure	Acronym	Meaning	Scoring
31-Item Rhinosinusitis Outcome Measuring Instrument[23]	RSOM-31	Lower score indicates better disease control	0 to 155
5-dimension EuroQol general health status visual analog scale[22]	EQ-5D-VAS	Higher score indicates better health status[a]	0 to 100
5-Item Asthma Control Questionnaire[30]	ACQ-5	Lower score indicates better asthma control	0 to 6
6-Item Asthma Control Questionnaire[10]	ACQ-6	Lower score indicates better asthma control	0 to 6
Asthma Quality of Life Questionnaire[30]	AQLQ	Higher score indicates better quality of life[b]	1 to 7
Chronis rhinosinusitis disease severity visual analog scale[21]	CRS VAS	Lower score indicates lower disease severity	0 to 10
Lund-Mackay CT score[24]	–	Higher score indicates higher opacification of the sinuses	0 to 24
Nasal Congestion Score[24]	NCS	Higher score indicates worse disease state status	0 to 3
Nasal Peak Inspiratory Flow[10,28]	NPIF[c]	Higher score indicates better nasal airflow	–
Nasal Polyp Score[10]	NPS	Higher score indicates worse disease state status	0 to 8

Measure	Acronym	Meaning	Scoring
Short-Form Health Questionnaire[28]	SF-36	Higher score indicated better QoL[d]	0 to 100
Sino-nasal Outcome Test (20 questions)[28]	SNOT-20	Lower score indicates better disease control and QoL	0 to 110
Sino-nasal Outcome Test (22 questions)[30]	SNOT-22	Lower score indicates better disease control and QoL[e]	0 to 112
Total Nasal Symptom Score[28]	TNSS	Higher score indicates worse health status	0 to 12
Total Polyp Score[23]	TPS	Higher score indicates worse disease state status	0 to 8
University of Pennsylvania Smell Identification Test[28]	UPSIT	Higher score indicates better sense of smell	0 to 40

Notes. [a] Minimal clinically important difference (MCID) = 8.45. [b] Clinically relevant change = 0.5. [c] Also known as Peak Nasal Inspiratory Flow (PNIF). [d] MCID = 3.8 for the physical component score (PCS) score; 4.6 for the mental component score (MCS); 5.5 for bodily pain domain; 7.0 for general health perceptions domain; 6.7 for mental health domain; 4.3 for physical functioning domain; 4.6 for role-emotional domain; 4 for role-physical domain; 6.2 for social functioning domain; 6.7 for vitality domain. [e] MCID = 8.9.
Abbreviations. CRS: chronic rhinosinusitis; CT: computed tomography; QoL: quality of life.

Omalizumab

Study Characteristics

We identified a total of 3 publications analyzing omalizumab for the treatment of CRS or CRSwNP: 1 report of 2 identical phase 3, multicenter, double-blind RCTs, and 2 randomized, double-blind RCTs.[23,24,28] No studies reported the impact of omalizumab on FEV-1. Efficacy outcomes included NPS, TPS, NCS, QoL measures, AQLQ, SF-36, SNOT-20, SNOT-22, and symptom control (31-item Rhinosinusitis Outcome Measuring Instrument [RSOM-31], TNSS, UPSIT, and Peak Nasal Inspiratory Flow [PNIF; also known as Nasal Peak Inspiratory Flow (NPIF)]).[23,24,28] Harm outcomes included incidence and severity of AEs. The studies enrolled adults aged 18 years and older (often with a maximum age of 75) with a serum IgE of 30 to 700 IU/mL, body mass of 30 kg to 50 kg, and a diagnosis of CRS[28] or CRSwNP.[24,28] One study excluded participants with recent use of systemic corticosteroids.[24] The RoB for the included studies were *low*, *medium*, and *high*.[23,24,28] Table 11 provides an overview of pertinent study characteristics, with additional study information provided in Appendix B, Table B1.

Table 11. Study Characteristics for Omalizumab in CRS or CRSwNP

Author, Year Registration Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Pinto et al., 2010[28] NCT00117611 Low	N = 14	Omalizumab SQ 0.016 mg/kg per IU serum IgE/mL every 2 or 4 weeks, n = 7 Placebo SQ every 4 weeks, n = 7	Randomized, double-blind, placebo-controlled	6 months

Author, Year Registration Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Gevaert et al., 2013[23] High	N = 24	Omalizumab SQ dose based on total serum IgE and body mass; max dose 375 mg every 2 or 4 weeks, n = 16 Placebo SQ, n = 8	Randomized, double-blind, placebo-controlled	16 weeks
Gevaert et al., 2020[24] NCT03280550 POLYP 1 NCT03280537 POLYP 2 Moderate	Total N = 265 POLYP 1, N = 138 POLYP 2, N = 127	Omalizumab SQ 75 to 600 mg every 2 to 4 weeks depending on pretreatment IgE and body mass, n = 134 Placebo SQ n = 131	2 identical phase 3 trials, randomized, double-blind, placebo-controlled	24 weeks

Abbreviations. CRS: chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyps; IgE: Immunoglobulin E; SQ: subcutaneous.

These studies evaluating omalizumab in participants with CRS or CRSwNP had sample sizes from 14 to 127, and follow-ups ranging from 16 weeks to 6 months (Table 11).[23,24,28] Each study enrolled adults aged 18 and older and examined the impact of subcutaneous (SQ) omalizumab (dosed by weight and serum IgE levels) versus placebo on markers of disease severity, symptoms, and QoL.[23,24,28]

Pinto and colleagues performed a small trial from 2004 to 2007 in participants with CRS that examined pretreatment and posttreatment sinus inflammation, determined by computerized tomography (CT) imaging (primary outcome), SF-36, SNOT-20, NPIF, UPSIT, TNSS, and nasal endoscopy scores.[28] In January 2007 to October 2008, Gevaert and colleagues compared omalizumab versus placebo in allergic (n = 13) and nonallergic (n = 11) participants with at least a 2-year history of CRSwNP.[23] The primary outcome was reduction in NPS after 16 weeks.[23] Secondary outcomes included changes in Lund-Mackay CT scores, sino-nasal and asthma symptoms (anterior rhinorrhea, loss of sense of smell, wheeze, dyspnea, cough, RSOM-31), spirometry, and QoL (SF-36, AQLQ).[23] A subsequent study by Gevaert and colleagues between November 2017 and March 2019 consisted of 2 identical phase 3 trials (POLYP 1 and POLYP 2) in participants with bilateral CRSwNP.[24] The primary outcomes were change from baseline in NPS and average daily NCS at 24 weeks.[24] Secondary outcomes included changes in SNOT-22, UPSIT, TNSS, AQLQ (participants with asthma [n = 151]), and symptoms (average daily sense of smell, postnasal drip, rhinorrhea); percentage of patients requiring systemic corticosteroids for 3 or more consecutive days, surgical polyp removal, or both at 24 weeks; and changes in NPS and NCS at 16 weeks.[24] Safety was also assessed through examination of vital signs, physical examination, laboratory evaluation, and AEs (see Appendix B, Table B3).[23,24,28]

Efficacy Outcomes

The certainty of evidence for omalizumab was rated as *low* to *moderate*. When compared to placebo, omalizumab demonstrated efficacy in improving QoL and symptomology in participants with CRS and CRSwNP. Table 12 provides a summary of GRADE findings for omalizumab.

Table 12. Summary of Findings (GRADE) for Omalizumab in CRS or CRSwNP

Outcome Studies Sample Size	Certainty of Evidence Treatment Groups	Relationship	Rationale
Change in NPS from baseline 2 RCTs[23,24] N = 303	Moderate Omalizumab vs. placebo	Omalizumab improved NPS compared to placebo	Downgraded 1 level for imprecision
Change in NCS from baseline 1 RCT[24] N = 265	Moderate Omalizumab vs. placebo	Omalizumab improved NCS compared to placebo	Downgraded 1 level for risk of bias
Change in SNOT-20 or SNOT-22 from baseline 2 RCTs[24,28] N = 279	Moderate Omalizumab vs. placebo	Omalizumab improved SNOT-22 score compared to placebo	Downgraded 1 level for imprecision
Change in SF-36 from baseline 2 RCTs[23,28] N = 38	Moderate Omalizumab vs. placebo	Omalizumab improved SF-36 score compared to placebo	Downgraded 1 level for imprecision
AEs 2 RCTs[23,24,28] N = 303	Moderate Omalizumab vs. placebo	Mild AEs were common but only common cold was found to occur more often in the treatment group than placebo	Downgraded 1 level for imprecision

Abbreviations. AE: adverse event; CRS: chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyps; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; NCS: Nasal Congestion Score; NPS: Nasal Polyp Score; RCT: randomized controlled trial; SF-36: 36-item Short-Form Health Questionnaire; SNOT-20: 20-item Sino-nasal Outcome Test; SNOT-22: 22-item Sino-nasal Outcome Test.

Gevaert and colleagues reported significant improvements in NPS and nasal polyp size in 2 studies.[23,24] Gevaert and colleagues found a significant polyp size reduction (−2.67; $P < .001$) in the omalizumab group, compared with no significant change in the placebo group.[23] There was a significant difference in NPS between the omalizumab and placebo groups starting at week 8 ($P = .03$) and continuing until study completion at 16 weeks ($P = .005$).[23] Gevaert and colleagues reported significant changes in NPS score at 24 weeks of −1.08 (POLYP 1) and −0.90 (POLYP 2) in the omalizumab groups compared the placebo groups, resulting in a difference between groups of −1.14 (95% CI, −1.59 to −0.69; $P < .01$) in POLYP 1 and −0.59 (95% CI, −1.05 to −0.12;

P = .01) in POLYP 2.[24] A 1 point or greater improvement in NPS was seen in 56.3 percent (72 of 128) of the omalizumab group versus 28.7 percent (15 of 129) of the placebo group.[24] Mean changes in NCS at 24 weeks were −0.89 (POLYP 1) and −0.70 (POLYP 2) for the omalizumab groups versus −0.35 (POLYP 1) and −0.20 (POLYP 2) in the placebo groups, resulting in differences of −0.55 (95% CI, −0.84 to −0.25; *P* < .001) in POLYP 1 and −0.50 (95% CI, 0.80 to −0.19; *P* = .002) in POLYP 2.[24] A 1-point or greater improvement in NCS was observed in 44.4% (56 of 126) of the pooled omalizumab group versus 21.4% (27 of 126) of the pooled placebo group.[24] Improvements in NPS and NCS were seen at 4 weeks and were similar at 16 weeks to changes seen at 24 weeks.[24] At 4 weeks, the average mean differences in NPS for the omalizumab group compared with placebo were −0.92 (95% CI, −1.37 to −0.48) in POLYP 1 and −0.52 (95% CI, −0.94 to −0.11) in POLYP 2.[24] The mean differences in NCS for the omalizumab group versus placebo at 4 weeks were −0.25 (95% CI, −0.46 to −0.04) in POLYP 1 and −0.26 (95% CI, −0.45 to −0.07) in POLYP 2.[24]

In the phase 3 trials published in 2020, Gevaert and colleagues reported use of omalizumab in patients with CRSwNP was associated with significant improvement in SNOT-22, UPSIT, TNSS, and nasal symptoms (loss of smell, postnasal drip, runny nose) at 24 weeks.[24] Mean differences between the omalizumab group versus the placebo group for POLYP 1 and POLYP 2 were −16.12 (95% CI, −21.86 to −10.38; *P* < .001) and −15.04 (95% CI, −21.26 to −8.82; *P* < .001) for SNOT-22; 3.81 (95% CI, 1.38 to 6.24; *P* = .002) and 3.86 (95% CI, 1.57 to 6.15; *P* = .001) for UPSIT; −1.91 (95% CI, −2.85 to −0.96; *P* < .001) and −2.09 (95% CI, −3.00 to −1.18; *P* < .001) for TNSS; −0.33 (95% CI, −0.60 to −0.06; *P* < .001) and −0.45 (95% CI, −0.73 to −0.16; *P* = .002) for loss of smell score; −0.56 (95% CI, −0.84 to −0.28; *P* < .001) and −0.54 (95% CI, −0.81 to −0.27; *P* < .001) for postnasal drip score; and −0.43 (95% CI, −0.70 to −0.16; *P* = .002) and −0.63 (95% CI, −0.90 to −0.35; *P* < .001) for runny nose score, respectively.[24] For participants with asthma, improvement in AQLQ score was more likely in the omalizumab group compared to placebo in both studies (POLYP 1: OR, 3.7; 95% CI, 1.0 to 13.7; *P* = .049; POLYP 2: OR, 4.0; 95% CI, 1.1 to 15.3; *P* = 0.04).[24]

Pinto and colleagues conducted a small RCT (N = 14) and found no difference between groups for nasal endoscopy scores (*P* < .58).[28] Pinto and colleagues reported a significant decrease in sinus inflammation in participants receiving omalizumab (n = 7; *P* < .04) but not in those receiving placebo. (n = 7; *P* < .46).[28] A clinically significant improvement in SNOT-20 was found in participants receiving omalizumab (mean = −1.05) points, but this change was not statistically significant.[28] There was a significant difference in the SF-36 domain of vitality (*P* < .05), but no difference between groups found for the other measured outcomes, likely due to the small sample size.[28] In the 2013 study by Gevaert and colleagues, symptom scores for nasal congestion (*P* = .002), anterior rhinorrhea (*P* = .003), loss of smell (*P* = .004), wheezing (*P* = .02), and dyspnea (*P* = .02) significantly improved.[23] There were no significant changes in cough or spirometry.[23] Sleep (*P* = .03) and general symptoms (RSOM-31; *P* = .01), improved in the omalizumab group only.[23] Total AQLQ improved in the omalizumab treatment group (*P* = .02) after 16 weeks of treatment with an improvement of 0.81 points compared to 0.27 points for the placebo group.[23] Significant improvements in the subdomains of the AQLQ for activity limitation (*P* = .002), symptoms (*P* = .01), and emotional function (*P* = .02) were found.[23] SF-36 significantly improved in the omalizumab group (*P* = .02) but not in the placebo group (*P* = .75).[23] A subgroup analysis of the omalizumab group demonstrated a significant improvement in AQLQ score for nonallergic

participants (−59.4; *P* = .03), but not in allergic participants (−12.3; *P* = .12).[23] There were no differences in the mean changes in SF-36 or RSOM-31 scores between allergic and nonallergic participants nor participants with or without aspirin hypersensitivity.[23]

Harm Outcomes

The studies by Gevaert and colleagues reported mild to moderate AEs in the majority (50.4% to 95.7%) of study participants, with only the common cold occurring significantly more often (*P* = .02) in the omalizumab treatment group in 1 of the 2 studies.[23,24] One participant in the placebo group in the 2013 study discontinued the study due to AEs (asthma attack).[23] The most common AEs were headache, nasopharyngitis, injection site reactions or pain, asthma exacerbation, arthralgia, back pain, dizziness, nose bleed, rhinitis, and sinusitis.[24] Most AEs occurred within 24 hours of drug administration and none were considered omalizumab-associated risks.[24] Three SAEs were reported in participants in the omalizumab group and 2 in the placebo group in the 2020 study.[24] No changes in vital signs, physical examination, or laboratory evaluation were found during the study period.[23] Pinto and colleagues reported no treatment-related AEs during the study period.[28]

Dupilumab

Study Characteristics

We identified a total of 6 publications analyzing dupilumab for the treatment of CRS and CRSwNP: 1 report of 2 multicenter, randomized, double-blind, RCTs with 1 subgroup analysis, 1 report of a randomized, double-blind RCT with 2 additional reports of study data, and a subgroup analysis of a randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial.[10,11,21,22,26,27] Efficacy outcomes included changes from baseline in NPS, NCS, AQLQ, FEV-1, SF-36, SNOT-22, UPSIT, NPIF, 5- and 6-question Asthma Control Questionnaire (ACQ-5, ACQ-6, respectively), Lund-Mackay CT score, 5-dimension EuroQol EQ-5D instrument visual analog scale (EQ-5D-VAS), CRS visual analog scale (CRS VAS), and clinical biomarkers. [10,11,21,22,26,27] Harm outcomes included incidence and severity of AEs. The studies enrolled adults aged 18 years and above with a diagnosis of CRS with or without nasal polyps, comorbid asthma, or both. We rated the RoB of included studies as *moderate*. We observed RoB concerns that included source of funding, and inconsistency (Table 14). Table 13 provides an overview of pertinent study characteristics, with additional study information provided in Appendix B, Table B1.

Table 13. Study Characteristics for Dupilumab in CRS or CRSwNP

Author, Year Registration Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Bachert et al., 2019[10] NCT02912468 SINUS-24 NCT02898454 SINUS-52 Moderate	SINUS-24, N = 276 SINUS-52, N = 448	Dupilumab 300 mg SQ every 2 weeks for 24 weeks; SINUS-24, n = 143 SINUS-52, n = 150 Dupilumab 300 mg SQ every 2 weeks for 24 weeks then every 4 weeks for 28 weeks; SINUS-52, n = 145 Matched placebo SQ; SINUS-24, n =133 SINUS-52, n = 153	Randomized, double-blind, placebo-controlled, parallel-group	SINUS-24: 48 weeks (24-week treatment period, 24-week follow-up period) SINUS-52: 64 weeks (52-week treatment period, 12-week follow-up period)
Fujieda et al., 2021[26] NCT02898454 Moderate	N = 45	Dupilumab 300 mg SQ every 2 weeks for 24 weeks, n = 16 Dupilumab 300 mg SQ every 2 weeks for 24 weeks then every 4 weeks for 28 weeks, n = 17 Placebo SQ, n = 16	Subgroup analysis of a randomized, double-blind, placebo-controlled, parallel-group	SINUS-52: 52 weeks
Maspero et al., 2020[27] NCT02414854 LIBERTY ASTHMA QUEST Moderate	N = 1902	Dupilumab 300 mg SQ every 2 weeks with a 600 mg loading dose, n = 633 Dupilumab 200 mg every 2 weeks with a 400 mg loading dose, n = 631 Matched placebo SQ n = 258	Subgroup analysis of a \randomized, double-blind, placebo-controlled, parallel-group	52 weeks
Bachert et al., 2016[11] NCT01920893 Moderate	N = 60	Dupilumab 300 mg SQ weekly for 15 weeks 600 mg loading dose, n = 30 Matched placebo SQ, n = 30	Randomized, double-blind, placebo-controlled, parallel-group	16 weeks

Author, Year Registration Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Bachert et al., 2019[22] Moderate	N = 60	Dupilumab 300 mg SQ weekly for 15 weeks 600 mg loading dose n = 30 Matched placebo SQ n = 30	Post hoc analysis of a randomized, double-blind, placebo-controlled, parallel-group trial	16 weeks
Bachert et al., 2020[21] NCT01920893 Moderate	N = 60	Dupilumab 300 mg SQ weekly for 15 weeks 600 mg loading dose, n = 30 Matched placebo SQ, n = 30	Post hoc analysis of a randomized, double-blind, placebo-controlled, parallel-group	16 weeks

Abbreviations. CRS: chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyps; SQ: subcutaneous.

The studies evaluating the use of dupilumab for CRS or CRSwNP had sample sizes ranging from 45 to 1,902 and follow-up periods of 16 to 64 weeks (Table 13).[10,11,27] All but 1 study[27] evaluated dupilumab in participants aged 18 and older; studies evaluated impacts of varied dosages and dosing intervals of dupilumab SQ versus matched placebos.[10,11,27] Two RCTs by Bachert and colleagues, run from August 2013 to August 2014 and from December 2016 to August 2017 enrolled participants with CRSwNP refractory to treatment with intranasal corticosteroids.[10,11] Primary outcomes included changes in NPS and nasal congestion severity; secondary outcomes included change in Lund-Mackay CT score, SNOT-22 score, UPSIT score, percentage of maxillary sinus volume occupied by disease, PNIF, patient-reported symptoms, symptom severity, FEV-1, ACQ-6, and safety and tolerability.[10,11] Two of the included studies are reports of secondary outcomes (e.g., EQ-5D-VAS, SF-36, ACQ-5), the presence of inflammatory markers (e.g., CRS VAS, SNOT-22, EQ-5D-VAS, SF-36), and the nasal polyp-related HealthCare Resource Utilization Questionnaire (HRUQ).[21,22] A subgroup analysis of Japanese participants in the LIBERTY NP SINUS-52 examined similar outcomes specifically in this population.[26] Maspero and colleagues performed a post hoc comparative analysis of participants with self-reported CRS versus participants without CRS in the Liberty Asthma Quest trial between April 2015 and July 2017.[31] Primary endpoints included change from baseline in prebronchodilator and postbronchodilator FEV-1 and annualized rate of asthma exacerbation.[27] Secondary outcomes included ACQ-5, AQLQ, SNOT-22 scores, biomarkers for inflammation, and the occurrence of AEs.[27] Additional study details can be found in Table 13 and Appendix B, Table B1.

Efficacy Outcomes

We rated the certainty of evidence for dupilumab as *moderate*. Overall, eligible studies showed that dupilumab demonstrated efficacy in improving spirometric measurements, symptoms, and QoL in participants with CRS or CRSwNP, compared with placebo. Table 14 provides a summary of GRADE findings for dupilumab.

Table 14. Summary of Findings (GRADE) for Dupilumab in CRSwNP

Outcome Studies Sample Size	Quality of Evidence Treatment Groups	Relationship	Rationale
Change from baseline in FEV-1 3 RCTs[10,11,27] N = 2,686	Moderate Dupilumab vs. placebo	Dupilumab inconsistently improved FEV-1 compared to placebo	Downgraded 1 level for inconsistency
Change in NPS from baseline 2 RCT[10,11] 1 subgroup analysis[26] N = 844	Moderate Dupilumab vs. placebo	Dupilumab improved NPS compared to placebo	Downgraded 1 level for risk of bias
Change in NCS from baseline 1 RCT[10] 1 subgroup analysis[26] N = 784	Moderate Dupilumab vs. placebo	Dupilumab improved NCS compared to placebo	Downgraded 1 level for risk of bias
Change in SNOT-22 from baseline 3 RCTs[10,11,27] 2 post hoc analyses[21,26] N = 2,686	Moderate Dupilumab vs. placebo	Dupilumab improved SNOT-22 score compared to placebo	Downgraded 1 level for risk of bias
AEs 2 RCTs[10,11] 1 subgroup analysis[26] N = 844	Moderate Dupilumab vs. placebo	Mild AEs were common but no differences were found between study groups	Downgraded 1 level for imprecision

Abbreviations. AEs: adverse events; CRSwNP: chronic rhinosinusitis with nasal polyps; FEV-1: forced expiratory volume in 1 second; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; NPS: Nasal Polyp Score; NCS: Nasal Congestion Score; RCT: randomized controlled trial; SNOT-22: 22-item Sino-nasal Outcome Test.

In 2016, Bachert and colleagues demonstrated the efficacy of dupilumab in decreasing NPS compared with placebo in 2 studies.[10,11] Fujieda and colleagues found that this efficacy was preserved in Japanese participants.[26] Mean change in NPS at 16 weeks was −1.9 (95% CI, −2.5 to −1.2) in the dupilumab group versus −0.3 (95% CI, −1.0 to −0.4) for the placebo group, resulting in a mean difference compared to placebo of −1.6 (95% CI, −2.4 to −0.7; $P < .001$).[11] A significant difference between groups was found at week 4.[11] NPS improvement of at least 1 point was demonstrated in 70% of the dupilumab group compared with 20% of placebo (OR, 9.5; 95% CI, 2.8 to 31.8; $P < .001$).[11] Based on the FEV-1 percent predicted, the mean change from baseline at 16 weeks was 9.0 (95% CI, 3.0 to 15.1) for the dupilumab group with mean difference versus placebo of 7.2 (95% CI, 0.4 to 13.9; $P = .04$), though no significant difference was found when measuring actual FEV-1.[11] SNOT-22 scores significantly improved in participants receiving dupilumab versus placebo (mean difference, −18.1; 95% CI, −25.6 to −10.6; $P < .01$).[11] They reported that dupilumab use resulted in significant improvement in QoL measures (SNOT-22, SF-36, ACQ-5, EQ-5D-VAS), symptoms (UPSIT, individual symptom scores), and surrogate markers

of disease (Lund-Mackay CT score, PNIF, disease occupancy of the maxillary sinus) from baseline to 16 weeks, compared to placebo.[11,21,22]

In the larger phase 3 follow-up trials, Bachert and colleagues reported significant improvements in FEV-1, symptoms, and QoL assessments at 24 weeks.[10] FEV-1 in the pooled analysis demonstrated a significant difference in the mean change from baseline of 0.21 (95% CI, 0.13 to 0.29; $P < .01$) in dupilumab versus placebo groups.[10] NPS was significantly improved at 24 weeks in the dupilumab groups (SINUS-24: mean difference, −2.06; 95% CI, −2.43 to −1.69; $P < .001$, SINUS-52: mean difference = −1.80; 95% CI, −2.10 to −1.51; $P < .001$).[10] At week 52, significant differences were found in the mean change from baseline in NPS (−2.40; 95% CI, −2.77 to −2.02; $P < .01$) and NCS (−0.98; 95% CI, −1.17 to −0.79; $P < .01$).[10] Forty-six percent (pooled n = 202) of the dupilumab group achieved at least a 2-point improvement in NPS at week 24 compared to 5% (n = 6) in SINUS-24 and 1% (n = 1) in SINUS-52.[10] Participants in the dupilumab group of the SINUS-52 trial demonstrated symptom improvement for the duration of the study, and discontinuation of study treatment at 24 weeks resulted in worsening symptoms.[10] In a subgroup analysis, Fujieda and colleagues found that this efficacy was preserved in Japanese participants.[26] Mean change in NPS at 16 weeks was −1.9 (95% CI, −2.5 to −1.2) in the dupilumab group versus −0.3 (95% CI, −1.0 to −0.4) for the placebo group, resulting in a mean difference compared to placebo of −1.6 (95% CI, −2.4 to −0.7; $P < .001$).[11] A significant difference between groups was found at week 4.[11] NPS improvement of at least 1 point was demonstrated in 70% of the dupilumab group compared with 20% of placebo (OR, 9.5; 95% CI, 2.8 to 31.8; $P < .001$).[11] Significant differences were found in dupilumab group versus placebo group for the change in ACQ-6 (−0.82; 95% CI, −0.98 to −0.67; $P < .01$), Lund-Mackay CT score ($P < .01$), total symptom score ($P < .01$), UPSIT ($P < .01$), loss of smell score ($P < .01$), and SNOT-22 score ($P < .01$) at 24 weeks.[10] At 52 weeks, the mean change in SNOT-22 in dupilumab versus placebo was (−20.96; 95% CI, −25.03 to −16.89; $P < .01$).[10] The proportion of patients with complete loss of smell decreased from baseline to 24 weeks in both studies, from 74% (n = 104) to 24% (n = 33) in SINUS-24 and from 79% (n = 228) to 30% (n = 84) in SINUS-52.[10] Participants in the dupilumab group of the SINUS-52 trial demonstrated symptom improvement for the duration of the study, and discontinuation of study treatment in SINUS-24 at 24 weeks resulted in worsening symptoms.[10]

Significant improvements in secondary outcomes including Lund-Mackay CT score, NCS, Total symptom score, PNIF, disease occupancy of the maxillary sinus, SNOT-22, UPSIT, EQ-5D-VAS and SF-36 domains general health, physical functioning, and vitality were achieved across the eligible studies in the dupilumab groups compared with placebo at all measured times ($P < .05$).[10,11,21,22,26] Significant improvements in symptoms including morning nasal congestion/obstruction and posterior rhinorrhea and symptom severity were demonstrated at 16 weeks ($P < .01$).[11] Participants in the dupilumab group were more likely ($P = .038$) to achieve the minimum clinically important difference in ACQ-5 scores versus the placebo group (62.5% vs. 15.8%, respectively) and demonstrated a significant score difference from baseline to 16 weeks versus placebo.[32] Participants in the dupilumab group were more likely to have a clinically meaningful improvement in SNOT-22 versus placebo (93.3% vs. 26.7%, respectively).[21] The SNOT-22 items that were most improved at week 16 correlated with the items that participants rated as most important to them and included sense of smell or taste, nasal blockage, thick nasal discharge, waking up tired, and fatigue.[21]

Maspero and colleagues reported significant improvements in spirometry and QoL for participants with and without self-reported CRS in the dupilumab group compared to placebo in the LIBERTY ASTHMA QUEST subgroup analysis.[27] Prebronchodilator FEV-1 significantly improved in all groups treated with dupilumab compared to placebo at 2 weeks (mean change, 0.20 L; 95% CI, 0.10 to 0.31; $P < .001$ for dupilumab 200 mg; 0.21 L; 95% CI, 0.11 to 0.31; $P < .001$ for dupilumab 300 mg), at 12 weeks (mean change, 0.18 L; 95% CI, 0.06 to 0.30; $P = .004$ for dupilumab 200 mg; 0.15 L; 95% CI, 0.04 to 0.27; $P = .01$ for dupilumab 300 mg), and at 52 weeks (mean change, 0.28 L; 95% CI, 0.15 to 0.41; $P < .001$ for dupilumab 200 mg; 0.16 L; 95% CI, 0.03 to 0.28; $P = .02$ for dupilumab 300 mg).[27] Findings were similar in participants without CRS.[27] Statistically significant changes in postbronchodilator FEV-1 were also found in all groups treated with dupilumab compared to placebo at 2 weeks (mean change, 0.20 L; 95% CI, 0.09 to 0.30; $P < .001$ for dupilumab 200 mg; 0.21 L; 95% CI, 0.11 to 0.31; $P < .001$ for dupilumab 300 mg), at 12 weeks (mean change, 0.12 L; 95% CI, 0.01 to 0.23; $P = .03$ for dupilumab 200 mg; 0.18 L; 95% CI, 0.07 to 0.28; $P < .001$ for dupilumab 300 mg), and at 52 weeks (mean change, 0.27 L; 95% CI, 0.15 to 0.39; $P < .001$ for dupilumab 200 mg; 0.14 L; 95% CI, 0.03 to 0.26; $P = .02$ for dupilumab 300 mg).[27] Treatment with dupilumab resulted in clinically and statistically significant improvements in ACQ-5 and AQLQ ($P < .05$) for both dupilumab 200 mg and 300 mg.

Harm Outcomes

In 2016, Bachert and colleagues reported AEs in 83.3% (25 of 30) of the placebo group and 100% of the dupilumab group.[11] Five participants in the placebo group and 2 participants in the dupilumab group withdrew from the study due to AEs.[11] In the SINUS-24 and SINUS-52 trials, Bachert and colleagues reported more AEs in the placebo group (74%, 6% serious) compared to the dupilumab group (69%, 3% serious; risk difference, −6.48; 95% CI, −13.04 to 0.08).[10] AEs caused discontinuation of 15 (5%) of participants in the placebo group compared to 11 (3%) in the treatment group.[10] Three participants receiving dupilumab experienced eosinophilia with clinical symptoms compared with 1 in the placebo group.[10] There were 2 deaths in the study, 1 in the treatment group and 1 in the placebo group, both unrelated to the study.[10] Seven participants in the dupilumab group and 1 in the placebo group reported nonserious cases of conjunctivitis.[10] In the subgroup analysis of Japanese participants, AEs occurred in 87.5% (n = 16) of placebo-treated participants, 81.5% (n = 16) of participants receiving dupilumab every 2 weeks for 52 weeks, and 100% (n = 17) of participants receiving dupilumab every 2 weeks for 24 weeks followed by dupilumab every four weeks for 28 weeks.[26] Maspero and colleagues reported similar rates of AEs (dupilumab group, 81.0% vs. placebo group, 83.1%).[27] The most common AEs were nasopharyngitis, asthma, nosebleed, headache, redness at the injection site, gastrointestinal disorder, influenza, and nasal polyps.[10,11,26,27] There were no SAEs reported in 3 of the included reports,[10,26,27]and the SAEs reported in the fourth report were not directly related to the use of dupilumab.[11]

Mepolizumab

Study Characteristics

We identified 3 publications analyzing mepolizumab for the treatment of CRSwNP; all were double-blind RCTs.[9,25,29] Efficacy outcomes included changes in TPS, NPS, nasal obstruction symptom VAS, SNOT-22, NPIF, ACQ-5, UPSIT, and need for nasal polyp removal surgery.[9,25,29]

Harm outcomes included incidence and severity of AEs.[9,25,29] The studies enrolled adults aged 18 and older with severe, bilateral nasal polyps recurrent after previous surgery.[9,25,29] We rated the RoB of included studies as *moderate* due to the role of the funding source. Table 15 provides an overview of pertinent study characteristics, with additional study information provided in Appendix B, Table B1.

Table 15. Study Characteristics for Mepolizumab in CRSwNP

Author, Year Registration Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Gevaert et al., 2011[29] CRT110178 Moderate	N = 30	Mepolizumab 750 mg IV given 2 times, 28 days apart, n = 20 Matched placebo IV, n = 10	Randomized, double-blind, placebo-controlled	48 weeks
Han et al., 2020[25] NCT03085797 SYNAPSE Moderate	N = 407	Mepolizumab 100 mg administered SQ every 4 weeks, n = 206 Placebo SQ every 4 weeks, n = 201	Phase 3, multicenter, randomized, double-blind, placebo-controlled, multicenter, parallel-group	52 weeks
Bachert et al., 2017[9] NCT01362244 Moderate	N = 107	Mepolizumab 750 mg administered by IV infusion every 4 weeks, n = 54 Placebo IV every 4 weeks, n = 51	Multicenter, randomized, double-blind, placebo-controlled	25 weeks

Abbreviations. CRS: chronic rhinosinusitis with nasal polyps; IV: intravenous; SQ: subcutaneous.

Gevaert and colleagues performed a double-blind, placebo-controlled RCT of mepolizumab in participants with primary grade 3 or grade 4 nasal polyps, or nasal polyps (grade 1 to grade 4) that recurred after surgery.[29] After a 4-week to 12-week run-in period, participants received either 2 single intravenous (IV) injections of 750 mg mepolizumab 28 days apart, or matched placebo.[29] The study enrolled 30 participants (mepolizumab, n = 20 vs. placebo, n = 10) who were followed for 48 weeks after receiving the first dose of the study medication.[29] The primary outcome was change in NPS at 8 weeks; other outcomes included changes in CT scan, NPIF, symptoms, clinical biomarkers, and safety.[29]

Han and colleagues performed a double-blind, multicenter, parallel-group, phase 3 RCT from May 2017 to December 2018 (SYNAPSE).[25] Participants were at least 18 years old, had severe, refractory, bilateral nasal polyp symptoms, and were eligible for repeat nasal surgery due to a nasal obstruction symptom VAS score of > 5 and NPS ≥ 5. After a 4-week run-in, participants received intranasal mometasone and either 100 mg mepolizumab SQ or placebo every 4 weeks

for 52 weeks.[25] Primary outcomes included change from baseline in NPS at 52 weeks and average nasal obstruction symptom VAS score in weeks 49 to 52.[25] Secondary outcomes included change from baseline to 52 weeks in SNOT-22, nasal obstruction symptom VAS score, proportion of participants requiring systemic corticosteroids, and time to first nasal surgery at 52 weeks.[25] Exploratory endpoints included proportion of participants achieving a decrease of 1 or more points in NPS at 52 weeks, a decrease of 8.9 points or more in the SNOT-22, change from baseline in UPSIT, and, in participants with asthma, the ACQ-5.[25]

Bachert and colleagues performed a double-blind, placebo-controlled, multicenter RCT between May 2009 and December 2014.[9] Study participants were aged 18 to 70 years with severe and recurrent bilateral nasal polyps refractory to intranasal steroid therapy and required to have surgery due to a NPS of 3 or greater in 1 nostril and at least 2 in the other, along with a VAS nasal symptom score of 7 or greater.[9] After a 10-day to 14-day run-in period, participants received 100 µg intranasal fluticasone in each nostril daily, plus either mepolizumab 750 mg or placebo, given by IV infusion every 4 weeks for 6 doses.[9] The primary outcome was the number of patients no longer requiring surgery 4 weeks after the last study dose. Secondary outcomes included the number of patients requiring surgery at each assessed time point, change from baseline to week 25 in TPS, symptom VAS scores, SNOT-22, EQ-5D, PNIF, Sniffin' Sticks Screening 12-test, FEV-1, peak expiratory flow rate, blood eosinophil counts, and pharmacokinetics, and safety.[9]

Efficacy Outcomes

We rated the certainty of evidence of relevant outcomes for mepolizumab in CRSwNP as *moderate.* Overall, eligible studies demonstrated efficacy of mepolizumab for improving NPS, TPS, and QoL (SNOT-22) with a low risk for AEs. Table 16 provides a summary of GRADE findings for mepolizumab.

Table 16. Summary of Findings (GRADE) for Mepolizumab in CRSwNP

Outcome Studies Sample Size	Certainty of Evidence Treatment Groups	Relationship	Rationale
Change in NPS from baseline 3 RCTs[9,25,29] N = 551	Moderate Mepolizumab vs. placebo	Mepolizumab improved NPS compared to placebo	Downgraded 1 level for risk of bias
Change in SNOT-22 from baseline 2 RCTs[9,25] N = 521	Moderate Mepolizumab vs. placebo	Mepolizumab improved SNOT-22 score compared to placebo	Downgraded 1 level for risk of bias
AEs 3 RCTs[9,25,29] N = 544	Moderate Mepolizumab vs. placebo	Mild AEs were common but no differences were found between study groups	Downgraded 1 level for imprecision

Abbreviations. AE: adverse event; CRSwNP: chronic rhinosinusitis with nasal polyps; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; RCT: randomized controlled trial; SNOT-22: 22-item Sino-nasal Outcome Test.

Gevaert and colleagues reported significant improvement in TPS.[29] At week 8, the change in TPS was −1.30 (standard deviation [SD], 1.72) resulting in difference versus placebo of −1.30 (SD, 1.51; *P* = .03).[29] The TPS improvement was 60 percent for mepolizumab versus 10 percent for placebo (OR, 13.5; *P* = .02).[29] CT scan score likewise improved over 50 percent in the mepolizumab group versus less than 20 percent in the placebo group, when rated by 3 independent raters (*P* = .06; *P* = .024; *P* = .049).[29] Improvements seen in symptoms and NPIF were not statistically significant.[29]

Han and colleagues reported significant improvements in the majority of measured endpoints favoring mepolizumab.[25] NPS improved by 1 point or more in 50 percent of participants in the mepolizumab group versus 28 percent in the placebo group at 52 weeks (OR, 2.74; 95% CI, 1.80 to 4.18; *P* < .001) and by 2 points or more in 36 percent of the mepolizumab group versus 13 percent in the placebo group at 52 weeks.[25] This was an average change of −0.9 (SD, 1.90) for mepolizumab and −0.1 (SD, 1.46) for placebo, and treatment effect of −0.73 (95% CI, −1.11 to −0.34; *P* < .001).[25] Nasal obstruction symptom VAS score improved during weeks 49 to 52 (−3.52; 95% CI, −4.09 to −2.18; *P* < .001) and 71 percent of the mepolizumab group and 50 percent of the placebo group had an improvement of at least 1 point.[25] SNOT-22 significantly improved in the mepolizumab group versus placebo at 52 weeks (treatment effect, −16.49; 95% CI, −23.57 to −9.42; *P* = .003) and 73 percent of mepolizumab group versus 54 percent placebo group achieved a score reduction of at least 8.9 points (*P* < .001).[25] There was no significant difference in UPSIT score change for mepolizumab versus placebo.[25]

Bachert and colleagues reported significant improvements in NPS and symptoms for participants in the mepolizumab group compared to placebo.[9] At 25 weeks, 50 percent (n = 27) of participants in the mepolizumab group compared to 27 percent (n = 14) in the placebo group achieved a 1-point or greater improvement in NPS.[9] The probability of having a reduction in NPS was higher in the mepolizumab group than the placebo group at weeks 9 and 25 (mepolizumab: OR, 5.6; 95% CI, 1.2 to 26.6; *P* = .03; placebo: OR, 6.6; 95% CI, 1.3 to 34.5; *P* = .03).[9] Average SNOT-22 improvements were greater in the mepolizumab group at 25 weeks, resulting in a treatment difference versus placebo of −13.2 (95% CI, −22.2 to −4.2; *P* = .005).[9] The mean difference in PNIF for mepolizumab versus placebo was significant at 26.7 (95% CI, 3.1 to 50.2; *P* = .03).[9] There was a significant reduction (*P* = .006) in the number of participants requiring surgery at 25 weeks with 30 percent (n = 16) no longer needing surgery in the mepolizumab group, versus 10 percent (n = 5) in the placebo group.[9] Nasal polyposis severity VAS score significantly improved in the mepolizumab group compared to placebo resulting in a treatment difference at 25 weeks of −1.8 (95% CI, −2.9 to −0.8; *P* = .001).[9] VAS scores for individual symptoms were likewise improved in the treatment group versus placebo at 25 weeks, and significant differences were seen as early 5 weeks for rhinorrhea and nasal blockage and 9 weeks for mucus and loss of smell.[9] There were no significant differences found for EQ-5D, EQ-5D-VAS, FEV-1, peak expiratory flow rate, or Sniffin' Sticks Screening 12-test.[9]

Harm Outcomes

Gevaert and colleagues reported at least 1 AE in 53 percent (16 of 30) of study participants, and 1 total SAE not related to the study treatment.[29] The most common AE was common cold, with 5 cases in the mepolizumab group versus 1 in the placebo.[29] No changes in vital signs, physical

examination, or clinical health markers were noted during the study period.[29] There was no significant difference in the occurrence of AEs between the mepolizumab and placebo groups.[29]

In the SYNAPSE trial, Han and colleagues found a similar rate of AEs in the mepolizumab (82%) versus placebo (84%) groups.[25] Study-related AEs were found in 15 percent in the mepolizumab group versus 9% in the placebo group.[25] The most common AEs were nasopharyngitis, sinusitis, headache, and nosebleed.[25] Serious adverse events occurred in 6 percent of participants in each group and were not considered related to study treatment.[25]

Bachert and colleagues found similar rates of AE between the mepolizumab and placebo groups.[9] The most common AEs were nasopharyngitis, headache, influenza, fever, back pain, and mouth pain, none of which were considered due to the study treatment.[9]

Ongoing Studies

We identified 7 ongoing studies that would potentially be eligible for this topic. Two of the studies assess dupilumab in CSU, 3 studies evaluate the use of dupilumab in the treatment of CRS without nasal polyps, and 2 studies evaluate treatment for CRSwNP (1 study with dupilumab and 1 with mepolizumab). Outcomes include symptom control, QoL measures, and AEs. No ongoing studies were found for the treatment of EGPA or HES. All of the studies are RCTs, with an enrollment target of 30 to 240 participants and estimated completion dates from April 2022 to December 2023. One study was originally scheduled to be completed in May 2021, but the last update provided with its progress was in August 2019. It is likely that this study has been delayed due to the current pandemic. Table 17 provides an overview of the ongoing studies.

Table 17. Ongoing Studies

Registration Number Study Title	Intervention and Comparator Condition(s) Study Design	Estimated Complete Date Enrollment	Outcomes
Chronic Spontaneous Urticaria (CSU)			
NCT04180488[33] Dupilumab for the Treatment of Chronic Spontaneous Urticaria in Patients Who Remain Symptomatic Despite the Use of H1 Antihistamines and Who Are Naïve to, Intolerant of, or Incomplete Responders to Omalizumab	Dupilumab Chronic spontaneous urticaria Randomized	April 2022 N = 234	• Change in ISS7, UAS7, AAS7, and weekly hives severity • Time to ISS7 MID • MID responders • Proportion of well controlled patients • OCS use during treatment • AEs • QoL
NCT03749135[34] Dupilumab in Chronic Spontaneous Urticaria	Dupilumab Chronic spontaneous urticaria; recurrent angioedema Randomized	May 2021 N = 72	• UAS7

Registration Number Study Title	Intervention and Comparator Condition(s) Study Design	Estimated Complete Date Enrollment	Outcomes
Chronic Rhinosinusitis Without Nasal Polyps			
NCT04362501[35] Efficacy of Dupilumab for Patients With Chronic Rhinosinusitis Without Nasal Polyps	Dupilumab Chronic sinusitis Randomized	October 2023 N =50	• SNOT-22 • Mini-RQLQ • UPSIT • Rescue medication • CT score • Rhinoscopy Score • Dropout rate • AEs
NCT04678856[36] Dupilumab in Chronic Rhinosinusitis Without Nasal Polyps	Dupilumab Chronic rhinosinusitis without nasal polyps; sinusitis; chronic sinusitis; sinus disorder; respiratory disorder Randomized	September 2023 N = 240	• LMK score • Anterior/posterior rhinorrhea severity score • Facial pain/pressure severity score • UPSIT • SNOT-22 • Rhinosinusitis severity VAS • FEV-1 • ACQ-6 • Annualized rate of systemic CS course • AEs
NCT04430179[37] Dupilumab Severe Eosinophilic Chronic Sinusitis Without Nasal Polyps	Dupilumab Severe eosinophilic chronic sinusitis without nasal polyposis Randomized	December 2022 N = 30	• LMK-CT score • Participant-reported symptoms score • VAS score • Nasal peak inspiratory flow • UPSIT score • SNOT-22 • Biomarker concentrations in nasal secretion
Chronic Rhinosinusitis With Nasal Polyps (CRSwNP)			
NCT04596189[38] Dupilumab for Prevention of Recurrence of CRSwNP After ESS	Dupilumab Chronic rhinosinusitis with nasal polyps Randomized	December 2022 N = 36	• Nonrecurrence of sinus cavity edema • Percentage with polyp recurrence • OCS use during treatment • Requiring re-operation for recurrence • Per-operative bleeding • Total nasal symptomatology • Nasal obstruction

Registration Number Study Title	Intervention and Comparator Condition(s) Study Design	Estimated Complete Date Enrollment	Outcomes
			• Nasal secretions • Facial pain • Rhinosinusitis severity VAS • CT scan opacification • Sense of smell • SNOT-22 • Asthma control
NCT04607005[39] Efficacy and Safety of Mepolizumab in Adults With Chronic	Mepolizumab Nasal polyps Randomized	February 2023 N = 160	• Total endoscopic NP score • Nasal obstruction VAS • SNOT-22 • Overall VAS symptom score • Mean composite VAS symptom score • LMK CT • Mean individual VAS symptom score • Time to first nasal surgery or course systemic CS

Abbreviations. AAS7: Weekly Angioedema Activity Score; ACQ-6: asthma control questionnaire 6 items; AE: adverse event; CS: corticosteroids; CT: computed tomography; ESS: endoscopic sinus surgery; FEV-1: forced expiratory volume; ISS7: Itch Severity Score over 7 days; LMK: Lund Mackay; MID: minimally important difference; NP: nasal polyp; OCS: oral corticosteroids; QoL: quality of life; RQLQ: rhinoconjunctivitis quality of life questionnaire; SNOT-22: Sino-Nasal Outcome Test-22 item; UAS7: Urticaria Activity Score summed over 7 days; UPSIT: University of Pennsylvania Smell Identification Test; VAS: visual analog scale.

Discussion

We identified and evaluated a number of RCTs on the treatment of the inflammatory conditions CSU, EGPA, HES, CRS, and CRSwNP with the monoclonal antibodies omalizumab, dupilumab, and mepolizumab. Availability of these studies were limited; for the rarest condition, EGPA, we only included 2 publications (1 RCT and 1 post hoc analysis). For the more common conditions (CRS/CRSwNP and CSU) we included 10 to 11 publications related to each condition for this topic. None of the studies included in the review included head-to-head comparisons of the biological medications of interest, or comparison to standard-of-care pharmacotherapy. The absence of comparative data prevents direct comparison of the included interventions. Overall, we generally rated the certainty of evidence for relevant outcomes as *moderate*.

The studies we identified for the treatment of CSU only investigated omalizumab. Though the mechanism of action is not entirely understood in the treatment of CSU, omalizumab therapy demonstrated improvement in both urticaria-related symptoms and QoL measurements when given to participants with refractory disease of up to 4 times the dose of standard H_1-antihistamines. The most common dosage associated with significant outcome improvements

was omalizumab 300 mg SQ, given every 4 weeks.[1,2,16] These studies mirrored the safety profile observed with monoclonal antibodies given for asthma, with no new concerns discovered. Omalizumab 150 mg to 300 mg demonstrated a promising pharmacotherapy option for those suffering from CSU.[1,2,16] Future studies of higher doses would need to be conducted to determine any additional benefit. Overall, we generally rated the certainty of evidence for relevant outcomes pertaining to CSU as *moderate*.

The studies we identified for the treatment of EGPA investigated mepolizumab. The current research, though scarce, suggests that mepolizumab could be used as add-on therapy to oral corticosteroids, with or without immunosuppressants, to cause disease remission or to delay relapse. A large portion of participants in both study groups experienced a relapse (56% in mepolizumab and 82% in placebo) and only 13% of the mepolizumab group had sustained remission for greater than 36 weeks.[5] The certainty of evidence for efficacy outcomes was generally *low*. Future research evaluating symptom relief, oral corticosteroid reduction, QoL, and the production and utilization of an EGPA-specific validation tool would be beneficial to determine the impact of monoclonal antibody use of in this rare patient population. Additionally, therapy optimization and improved outcomes might be achieved through determination of the relationship between drug dosage and participant response.

Few studies were found for the treatment of HES with monoclonal antibodies. Of the studies we identified, only mepolizumab was investigated. The specificity of mepolizumab binding to IL-5 seems to make it an ideal therapy when targeting eosinophilic diseases such as HES. This is supported by clinical trials demonstrating a reduction in oral corticosteroid use and flare occurrence, each of which can have a significant impact on QoL.[6] With no SAEs and minimal drug-related AEs reported, mepolizumab is a favorable pharmacotherapy option for those suffering from uncontrolled HES. Overall, we generally rated the certainty of evidence for relevant outcomes pertaining to HES as *moderate*.

Studies evaluating the impact of biologic drugs on outcomes of CRS and CRSwNP are limited, making it difficult to compare interventions. For this review, we identified 12 total studies, 3 RCTs for omalizumab, 3 RCTs and 2 post hoc analyses and 1 subgroup analysis for dupilumab, and 3 RCTs for mepolizumab. Generally, we rated the certainty of evidence of relevant outcomes as *low* to *moderate*. Only two studies included CRS and did not distinguish between outcomes for individuals with and without nasal polyps.[27,28] Few trials investigated the impact of biological drugs on FEV-1 in individuals with CRS. In these studies, this outcome was examined as either a secondary or exploratory endpoint. Medication impact on symptomology and QoL is more readily available, though the number of studies per biologic medication is limited. Though there were mixed results, larger studies demonstrated efficacy in the improvement of FEV-1 when administering dupilumab SQ 200 mg or 300 mg every 2 weeks for up to 52 weeks compared to placebo, especially in individuals considered nonallergic.[10,27] Dupilumab therapy had a low risk of mild AEs, and was not associated with SAEs in any of the available studies.[10,11,27] Due to a lack of RCTs for omalizumab and mepolizumab, no definitive conclusions can be drawn about their impact on FEV-1. Further studies are needed to determine the impact of omalizumab and mepolizumab on FEV-1 and the impact of each of these therapies on the symptoms and QoL for individuals with less severe disease.

Omalizumab, dupilumab, and mepolizumab therapies were shown to improve NPS, symptoms, and QoL in individuals with nasal polyps. NCS improved for participants treated with omalizumab or dupilumab, but there were no studies assessing the impact of mepolizumab on this outcome.[10,24,26] Results were mixed for improvement in sense of smell (measured by UPSIT score) by omalizumab, and no improvement was found for mepolizumab (measured by Sniffin' Sticks Screening 12-test).[9] Dupilumab therapy demonstrated improvement in UPSIT in the 1 RCT available.[26] Omalizumab and dupilumab therapies were also associated with improvements in the AQLQ and SF-36 QoL measures.[27] QoL according to SNOT-20 and SNOT-22 scores consistently improved with each of the 3 therapies.[9,11,24-26,28] No significant change in QoL was found for mepolizumab utilizing the EQ-5D and EQ-5D-VAS scales.[9] For individuals with CRSwNP, treatment with omalizumab, dupilumab, or mepolizumab is likely to positively impact NPS and associated symptoms. Omalizumab and dupilumab are likely to improve NCS, and disease state-related QoL will likely improve during treatment with any of the 3 drugs. Further studies are needed to determine the impact of mepolizumab on additional indicators of disease symptomology, the comparison of these treatments versus standard therapy, and the impact on mild to moderate disease including CRS without nasal polyps.

Indications for the use of omalizumab, dupilumab, and mepolizumab for nonasthma inflammatory conditions are expanding. Ongoing studies are currently examining the impact of these medications on additional measures of symptom control and QoL, as well as the use in conditions for which they are not currently indicated. It is anticipated that study of these medications in similar conditions will continue based on their efficacy and safety profiles, though head-to-head comparisons of these medications are unlikely.

References

1. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol.* 2015;135(1):67-75. doi: 10.1038/jid.2014.306.

2. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med.* 2013;368(10):924-935. doi: 10.1056/NEJMoa1215372.

3. Staubach P, Metz M, Chapman-Rothe N, et al. Effect of omalizumab on angioedema in H1 -antihistamine-resistant chronic spontaneous urticaria patients: results from X-ACT, a randomized controlled trial. *Allergy.* 2016;71(8):1135-1144. doi: 10.1111/all.12870.

4. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol.* 2013;132(1):101-109. doi: 10.1016/j.jaci.2013.05.013.

5. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med.* 2017;376(20):1921-1932. doi: 10.1056/NEJMoa1702079.

6. Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med.* 2008;358(12):1215-1228. doi: 10.1056/NEJMoa070812.

7. Roufosse F, Kahn JE, Rothenberg ME, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. *J Allergy Clin Immunol.* 2020;146(6):1397-1405. doi: 10.1016/j.jaci.2020.08.037.

8. Chong LY, Piromchai P, Sharp S, et al. Biologics for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2021(3). doi: 10.1002/14651858.CD013513.pub3.

9. Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. *J Allergy Clin Immunol.* 2017;140(4):1024-1031.e1014. doi: 10.1016/j.jaci.2017.05.044.

10. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet.* 2019;394(10209):1638-1650. doi: 10.1016/S0140-6736(19)31881-1.

11. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *Jama*. 2016;315(5):469-479. doi: 10.1001/jama.2015.19330.

12. Kahwati L, Chang E, Rains C, Fortman R, Kennedy S, Gartlehner G. *Biologics to treat asthma and chronic spontaneous urticaria: update.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2021.

13. Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128(1):202-209.e205. doi: 10.1016/j.jaci.2011.04.038.

14. Staubach P, Metz M, Chapman-Rothe N, et al. Omalizumab rapidly improves angioedema-related quality of life in adult patients with chronic spontaneous urticaria: X-ACT study data. *Allergy*. 2018;73(3):576-584. doi: 10.1111/all.13339.

15. Metz M, Staubach P, Bauer A, et al. Clinical efficacy of omalizumab in chronic spontaneous urticaria is associated with a reduction of FcepsilonRI-positive cells in the skin. *Theranostics*. 2017;7(5):1266-1276. doi: 10.7150/thno.18304.

16. Hide M, Park HS, Igarashi A, et al. Efficacy and safety of omalizumab in Japanese and Korean patients with refractory chronic spontaneous urticaria. *J Dermatol Sci*. 2017;87(1):70-78. doi: 10.1016/j.jdermsci.2017.03.009.

17. Hide M, Igarashi A, Yagami A, et al. Efficacy and safety of omalizumab for the treatment of refractory chronic spontaneous urticaria in Japanese patients: Subgroup analysis of the phase 3 POLARIS study. *Allergol*. 2018;67(2):243-252. doi: 10.1016/j.alit.2017.10.001.

18. Casale TB, Murphy TR, Holden M, Rajput Y, Yoo B, Bernstein JA. Impact of omalizumab on patient-reported outcomes in chronic idiopathic urticaria: Results from a randomized study (XTEND-CIU). *J Allergy Clin Immunol Pract*. 2019;7(7):2487-2490.e2481. doi: 10.1016/j.jaip.2019.04.020.

19. Steinfeld J, Bradford ES, Brown J, et al. Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. *J Allergy Clin Immunol*. 2019;143(6):2170-2177. doi: 10.1016/j.jaci.2018.11.041.

20. Roufosse F, de Lavareille A, Schandene L, et al. Mepolizumab as a corticosteroid-sparing agent in lymphocytic variant hypereosinophilic syndrome. *J Allergy Clin Immunol*. 2010;126(4):828-835.e823. doi: 10.1016/j.jaci.2010.06.049.

21. Bachert C, Hellings PW, Mullol J, et al. Dupilumab improves health-related quality of life in patients with chronic rhinosinusitis with nasal polyposis. *Allergy*. 2020;75(1):148-157. doi: 10.1111/all.13984.

22. Bachert C, Hellings PW, Mullol J, et al. Dupilumab improves patient-reported outcomes in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma. *J Allergy Clin Immunol Pract*. 2019;7(7):2447-2449.e2442. doi: 10.1016/j.jaip.2019.03.023.

23. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013;131(1):110-116.e111. doi: 10.1016/j.jaci.2012.07.047.

24. Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. 2020;146(3):595-605. doi: 10.1016/j.jaci.2020.05.032.

25. Han J, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps. *American Rhinologic Society 66th Annual Meeting*. 2020; https://www.american-rhinologic.org/assets/docs/Meetings/2020_Annual/2020%20ARS%20Annual%20-%20Full%20Program.pdf. Accessed 10/13/2021.

26. Fujieda S, Matsune S, Takeno S, et al. The effect of dupilumab on intractable chronic rhinosinusitis with nasal polyps in Japan. *Laryngoscope*. 2021;131(6):E1770-E1777. doi: 10.1002/lary.29230.

27. Maspero JF, Katelaris CH, Busse WW, et al. Dupilumab efficacy in uncontrolled, moderate-to-severe asthma with self-reported chronic rhinosinusitis. *J Allergy Clin Immunol Pract*. 2020;8(2):527-539.e529. doi: 10.1016/j.jaip.2019.07.016.

28. Pinto JM, Mehta N, DiTineo M, Wang J, Baroody FM, Naclerio RM. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. *Rhinology*. 2010;48(3):318-324. doi: 10.4193/Rhino09.144.

29. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol*. 2011;128(5):989-995.e981-988. doi: 10.1016/j.jaci.2011.07.056.

30. Maspero J, Bachert C, Canonica G, et al. Efficacy of dupilumab in chronic rhinosinusitis with nasal polyps and comorbid asthma by baseline biomarkers of type 2 inflammation: SINUS-24 and SINUS-52 phase 3 trials. *Clin Exp Allergy*. 2021;51(1):173-174.

31. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-2496. doi: 10.1056/NEJMoa1804092.

32. Bachert C, Zinreich SJ, Hellings PW, et al. Dupilumab reduces opacification across all sinuses and related symptoms in patients with CRSwNP. *Rhinology*. 2020;58(1):10-17. doi: 10.4193/Rhin18.282.

33. ClinicalTrials.gov. Dupilumab for the treatment of chronic spontaneous urticaria in patients who remain symptomatic despite the use of H1 antihistamine and who are naïve to, intolerant of, or incomplete responders to omalizumab. 2019; https://ClinicalTrials.gov/show/NCT04180488. Accessed September 3, 2021.

34. ClinicalTrials.gov. Dupilumab in chronic spontaneous urticaria. 2018; https://ClinicalTrials.gov/show/NCT03749135. Accessed September 3, 2021.

35. ClinicalTrials.gov. Efficacy of dupilumab for patients with chronic rhinosinusitis without nasal polyps (CRSsNP). 2020; https://ClinicalTrials.gov/show/NCT04362501. Accessed September 3, 2021.

36. ClinicalTrials.gov. Dupilumab in CRSsNP. 2020; https://ClinicalTrials.gov/show/NCT04678856. Accessed September 3, 2021.

37. ClinicalTrials.gov. Dupilumab severe eosinophilic chronic sinusitis without nasal polyposis. 2020; https://ClinicalTrials.gov/show/NCT04430179. Accessed September 3, 2021.

38. ClinicalTrials.gov. Dupilumab for prevention of recurrence of CRSwNP after ESS. 2021; https://ClinicalTrials.gov/show/NCT04596189. Accessed September 3, 2021.

39. ClinicalTrials.gov. Efficacy and safety of mepolizumab in adults with chronic rhinosinusitis With nasal polyps (CRSwNP)/ eosinophilic chronic rhinosinusitis (ECRS). 2021; https://ClinicalTrials.gov/show/NCT04607005. Accessed September 3, 2021.

40. Scottish Intercollegiate Guidelines Network. Methodology checklist 2: randomised controlled trials. 2015; http://www.sign.ac.uk/checklists-and-notes.html. Accessed May 9, 2017.

41. National Heart, Lung, and Blood Institute,. Quality assessment tool for before-after (pre-post) studies with no control group. 2018; https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed April 27, 2017.

42. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi: 10.1136/bmj.39489.470347.AD.

43. Schünemann H, Brozek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. 2014; http://gdt.guidelinedevelopment.org/app/handbook/handbook.html. Accessed December 15, 2015.

Appendix A. Methods

We followed standard Drug Effectiveness Review Project (DERP) methods and procedures for performing systematic reviews. We searched Ovid MEDLINE, the Cochrane Library, Google Scholar, and other evidence sources up through July 5, 2021. Ongoing studies were identified through ClinialTrials.gov, the International Standard Randomized Controlled Trials Number (ISRCTN) registry, and US Food and Drug Administration (FDA) resources. We selected studies for inclusion if they met our PICOS, were conducted in human participants, and were published in English. Systematic reviews were not included, but the reference lists of these reviews were used to identify additional studies.

We also used the following search terms for Google, Google Scholar, and additional DERP evidence sources:

- chronic rhinosinusitis, chronic spontaneous urticarial, CSU, eosinophilic granulomatosis, hypereosinophilic, nasal polyp
- dupilumab, dupixent, mepolizumab, nucala, omalizumab, xolair
- random, randomized, RCT

Ovid MEDLINE

Database: Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to July 02, 2021>

Search Strategy:

1 Omalizumab

2 (dupilumab or dupixent or mepolizumab or nucala or omalizumab or xolair).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3 1 or 2

4 Rhinitis/ or Sinusitis/ or Nasal Polyps/

5 Chronic Urticaria/

6 Eosinophilia/ or Churg-Strauss Syndrome/ or Eosinophilic Granuloma/

7 exp Hypereosinophilic Syndrome/

8 (chronic rhinosinusitis or chronic spontaneous urticaria or CSU or eosinophilic

1. granulomatosis or churg-strauss or hypereosinophilic or nasal polyp*).tw.

9 4 or 5 or 6 or 7 or 8

10 3 and 9

11 limit 10 to (english language and randomized controlled trial)

Cochrane Library Search

Searched using Title/Abstract/Keyword:
(dupilumab or dupixent or mepolizumab or nucala or omalizumab or Xolair) AND (chronic rhinosinusitis OR chronic spontaneous urticaria OR eosinophilic granulomatosis OR hypereosinophilic OR churg-strauss OR nasal polyp*)

Ongoing Studies

We searched the following DERP sources for ongoing studies using search strategies as noted:

- ClinicalTrials.gov (conducted on July 5, 2021)
  - chronic rhinosinusitis OR chronic spontaneous urticaria OR eosinophilic granulomatosis OR hypereosinophilic OR churg-strauss OR nasal polyp*) | (dupilumab OR mepolizumab OR omalizumab
- ISRCTN Registry (conducted on July 5, 2021)
  - mepolizumab
  - dupilumab
  - omalizumab
- FDA resources (conducted on July 5, 2021)
  - dupilumab or dupixent or mepolizumab or Nucala or omalizumab or Xolair

Screening

Two experienced researchers independently screened all titles and abstracts of identified documents. In cases in which there was disagreement about eligibility, a third experienced researcher resolved the disagreement. This method was repeated for full-text review of documents that could not be excluded by title and abstract screening.

Risk of Bias Assessment

Risk of Bias of Included Studies

We assessed the RoB of the included RCTs and uncontrolled studies using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for quality.[40,41] Two experienced researchers independently rated all included studies. In cases in which there was disagreement about the RoB of a study, a third rater resolved the disagreement.

Randomized Controlled Trials

Low-risk-of-bias randomized controlled trials include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Low-risk-of-bias randomized controlled trials also have low potential for bias from conflicts of interest and funding source(s). Moderate-risk-of-bias randomized controlled trials have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High-risk-of-bias randomized controlled trials have clear flaws that could introduce significant bias.

Overall Quality of Evidence

We assigned each outcome a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group.[42,43] Two independent experienced researchers assigned ratings, with disagreements resolved by a third rater. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are randomized controlled trials with few or no limitations, and the estimate of effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are randomized controlled trials with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are randomized controlled trials with serious limitations or nonrandomized studies without special strengths.
- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

Appendix B. Full Evidence Tables

Table B1. Study Design, Demographics, and Quality Ratings

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
Chronic Spontaneous Urticaria		
Maurer et al., 2011[13] 16 centers in Germany Novartis Moderate	Randomized, double-blind, placebo-controlled, parallel-group Omalizumab (75 to 375 mg) SQ every 2 to 4 weeks based on weight total serum IgE at screening, n = 27 Placebo SQ every 2 to 4 weeks, n = 22 Total, N = 49	Age (mean): 40.5 years Male: 22.4% White: 100% Weight (kg), mean ± SD: • Omalizumab: 81.9 ± 20.2 • Placebo: 71.2 ± 12.4 IgE-anti-TPO (IU/mL), mean ± SD: • Omalizumab: 7.3 ± 4.6 • Placebo: 6.2 ± 3.7 Total IgE (IU/mL), mean ± SD: • Omalizumab: 211 ± 158 • Placebo: 181 ± 136 <u>Inclusion Criteria</u> • 18 to 70 years old • Diagnosis of moderate-to-severe CSU • Weigh between 20 – 150 kg • Total serum IgE-anti-TPO antibody level of ≥ 5.0 IU/mL 3 months • ≥ 10 UAS7[b] score

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		Exclusion Criteria • Acute urticaria • Chronic diarrhea • Severe renal dysfunction • Increased serum IgE not attributed to allergies or urticaria • History of epilepsy, allergy to antibiotics, malignancy within past 5 years, CVA attacks/ischemia • Taking any immunosuppressant medications, including oral or parenteral corticosteroids, methotrexate, or cyclosporine in the 4 weeks prior to screening.
Maurer et al., 2013[2] NCT01292473 ASTERIA II Genentech and Novartis Pharma Moderate	International, multicenter, randomized, double-blind, placebo-controlled Omalizumab SQ every 4 weeks • 75 mg, n = 82 • 150 mg, n = 83 • 300 mg, n = 79 Placebo SQ every 4 weeks, n = 79 N = 323	Age (mean ± SD): 42.5 ± 13.7 years Male: 24% White: 85% Weight (mean): 82.4 kg BMI (mean ± SD): 29.8 ± 7.3 kg/m^2 IgE level (mean ± SD): 168.2 ± 231.9 IU/mL Time since diagnosis (mean ± SD): 6.5 ± 8.6 years In-clinic UAS[a] (mean ± SD): 5.3 ± 0.7 UAS7[b] (mean ± SD): 30.7 ± 6.8 ISS7[c] (mean ± SD): 14 ± 3.7

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		Weekly number of hives (mean ± SD): 16.7 ± 4.3 Use of rescue medication per week (mean ± SD): 7.3 ± 7.8 <u>Inclusion Criteria</u> • 12 to 75 years (18 to 75 years in Germany) • History of ≥ 6 months of CU • Presence of hive (with itching) ≥ 8 weeks before enrollment, consecutively, while on H_1-antihistamines • UAS7 of ≥ 16 • ISS7 of ≥ 8 • 3 days of second generation H_1-antihistamine directly prior screening • No missing diary entries for 7 days prior to randomization <u>Exclusion Criteria</u> • Known cause for chronic urticaria • Routine administration of immunosuppressant drugs within previous 30 days • Use of a H_2-antihistamine or LTRA • Use of greater-than-licensed doses of H_1-antihistamines 3 days prior to screening • History of cancer or hypersensitivity to omalizumab • Treatment with omalizumab within past year • Weight < 20 kg • Pregnant

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
Kaplan et al., 2013[4] NCT01264939 GLACIAL 65 centers Genentech and Novartis Pharma Moderate	Global phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group Omalizumab 300 mg SQ every 4 weeks, n = 252 Placebo SQ every 4 weeks, n = 84 N = 336	Age (mean): 43.1 years Male: 28.1% White: 89% BMI (mean): 29.8 kg/m^2 Total IgE level (mean): 158.5 IU/mL Time since diagnosis (mean): 7.4 years In-clinic UAS[a] (mean): 5.2 UAS7[b] (mean): 30.9 ISS7[c] (mean): 14 Weekly number of hives: 16.9 Presence of angioedema: 53.1% <u>Inclusion Criteria</u> • 12 to 75 years (18 to 75 years in Germany) • History of ≥ 6 months of CU • Presence of hive (with itching) ≥ 6 weeks before enrollment, consecutively, while on H_1-antihistamines plus H_2-antihistamines, LTRAs, or both • UAS7 of ≥ 16 • Weekly itch-severity of ≥ 8 • In-clinic UAS of ≥ 4

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• No missing diary entries for 7 days prior to randomization <u>Exclusion Criteria</u> • Known cause for chronic urticaria • Routine administration (≥ 5 consecutive days) of immunosuppressant drugs (systemic corticosteroids, hydroxychloroquine, methotrexate, etc.) within previous 30 days • History of cancer or hypersensitivity to omalizumab • Treatment with omalizumab within past year • Pregnant, childbearing age (with lack of acceptable contraception), or breastfeeding
Saini et al., 2015[1] NCT01287117 ASTERIA I 53 centers in Denmark, France, Germany, Italy, Poland, Spain, Turkey, and the United States Genentech and Novartis Pharma Moderate	Randomized, double-blind, placebo-controlled Omalizumab SQ every 4 weeks • 300 mg, n = 81 • 150 mg, n = 80 • 75 mg, n = 78 Placebo SQ every 4 weeks, n = 80 N = 319	Age (mean), years: • Omalizumab 300 mg: 42.4 • Omalizumab 150 mg: 41.1 • Omalizumab 75 mg: 40.7 • Placebo: 40.4 Male (mean), %: • Omalizumab 300 mg: 25.9 • Omalizumab 150 mg: 20 • Omalizumab 75 mg: 25.9 • Placebo: 35 White (mean), %: • Omalizumab 300 mg: 91.4 • Omalizumab 150 mg: 78.8 • Omalizumab 75 mg: 80.5 • Placebo: 80

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		BMI (mean), kg/m^2: • Omalizumab 300 mg: 29.3 • Omalizumab 150 mg: 29.8 • Omalizumab 75 mg: 29.4 • Placebo: 28.7 Time since diagnosis (mean), years: • Omalizumab 300 mg: 6.2 • Omalizumab 150 mg: 7.6 • Omalizumab 75 mg: 7.0 • Placebo: 7.0 In-clinic UAS[a] (mean): • Omalizumab 300 mg: 5.3 • Omalizumab 150 mg: 5.3 • Omalizumab 75 mg: 5.3 • Placebo: 5.3 UAS7[b] (mean): • Omalizumab 300 mg: 31.3 • Omalizumab 150 mg: 30.3 • Omalizumab 75 mg: 31.7 • Placebo: 31.1 ISS7[c] (mean): • Omalizumab 300 mg: 14.2 • Omalizumab 150 mg: 14.1 • Omalizumab 75 mg: 14.5 • Placebo: 14.4 Weekly number of hives score (mean):

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• Omalizumab 300 mg: 17.1 • Omalizumab 150 mg: 16.2 • Omalizumab 75 mg: 17.2 • Placebo: 16.7 Overall DLQI[d] score (mean): • Omalizumab 300 mg: 13.0 • Omalizumab 150 mg: 13.6 • Omalizumab 75 mg: 12.8 • Placebo: 14.0 Angioedema present (mean), %: • Omalizumab 300 mg: 42.0 • Omalizumab 150 mg: 47.5 • Omalizumab 75 mg: 45.5 • Placebo: 55.0 <u>Inclusion Criteria</u> • 12 to 75 years • CIU/CSU (≥ 6 months with hives/itching for ≥ 8 consecutive weeks) despite appropriate H_1-antihistamines at approved doses • In-clinic UAS ≥ 4 • UAS7 ≥ 16; itch component ≥ 8 <u>Exclusion Criteria</u> • Clearly defined cause for CU • Diseases with urticaria or angioedema • Routine doses of immunosuppressants • Weight < 20 kg

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• Hypersensitivity to omalizumab or treatment with it within previous year
Staubach et al., 2016[3] Staubach et al., 2018[14] NCT01723072 X-ACT 24 centers in Germany Novartis Pharma Moderate	Double-blind, placebo-controlled, randomized, multicenter Omalizumab (150 mg x 2) SQ every 4 weeks, n = 44 Placebo SQ every 4 weeks, n = 47 N = 91	Age (mean), years: • Omalizumab: 44.9 • Placebo: 41.1 Male (mean), %: • Omalizumab: 31.8 • Placebo: 29.8 White (mean), %: • Omalizumab: 95.5% • Placebo: 97.9 Duration of disease state (mean ± SD), year: • Omalizumab: 8.4 ± 9.3 • Placebo: 7.4 ± 8.8 CU-Q_2oL[e] score (mean ± SD): • Omalizumab: 55.4 ± 13.6 • Placebo: 56.1 ± 17.2 DLQI[d] score (mean ± SD): • Omalizumab: 14.6 ± 5.7 • Placebo: 16.6 ± 7.3 UAS7[b] (mean ± SD): • Omalizumab: 26.5 ± 8.2 • Placebo: 27.9 ± 8.7 AAS[f] (mean ± SD):

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• Omalizumab: 22.5 ± 20.6 • Placebo: 28.1 ± 24.1 <u>Inclusion Criteria</u> • 18 – 75 years old • Wheals present and ≥ 4 angioedema occurrences within last ≥ 6 months • Symptomatic despite high antihistamine treatment • UAS7 ≥ 14 • CU-Q_2oL[e] score ≥ 30 <u>Exclusion Criteria</u> • Non-urticaria-associated angioedema • H_1-antihistamines ≥ 4 times approved dose 3 days prior to day 14 • H_2-antihistamines or LRTAs ≤ 7 days prior to day 14 • Immunosuppressant medications ≤ 30 days prior to day 14 • Serious psychological disturbances • Metabolic and pathological conditions • History of malignancy or hypersensitivity to study drug • Treatment with study drug within ≤ 6 months • Pregnant or breastfeeding
Metz et al., 2017[15] NCT01599637 4 centers in Germany Novartis and Genentech Moderate	Exploratory, double-blind, parallel group, randomized, placebo-controlled Phase II study Omalizumab 300 mg SQ every 4 weeks, n = 20 Placebo SQ every 4 weeks, n = 10	Age (mean): 38.7 years Male (mean): 13% White (mean): 100% BMI (mean): 27.7 kg/m^2

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
	N = 30	Baseline UAS7[b] (mean): • Omalizumab 300 mg: 32.2 • Placebo: 31.6 <u>Inclusion Criteria</u> • 18 to 75 years • ≥ 6 months of CSU diagnosis • Symptomatic CSU despite H_1-antihistamine approved treatment doses • Itch and hives present for ≥ 6 weeks prior to baseline • UAS7 ≥ 16; itch component of ≥ 8 fourteen days prior to randomization <u>Exclusion Criteria</u> • Weight > 130 kg or < 40 kg • Heavy smoking • Chronic urticaria (other than CSU) • Disease with symptoms of urticaria or angioedema • History or presence of atopic dermatitis, bullous pemphigoid, dermatitis, herpetiformis, senile pruritus, or other skin diseases associated with itch • Signs of parasitic infection • Asthma and atopic dermatitis • History of hypersensitivity to omalizumab or similar, local anesthetics, or anaphylactic shock
Hide et al., 2017[16] NCT02329223 POLARIS 41 sites in Japan and Korea	Randomized, double-blind, placebo-controlled, parallel-group multicenter phase 3 study Omalizumab SQ every 4 weeks • 150 mg, n = 71	Age (mean), years: • Omalizumab 300 mg: 44.6 • Omalizumab 150 mg: 43.6 • Placebo: 42.5 Male (mean), %:

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
Novartis Pharmaceuticals Moderate	• 300 mg, n = 73 Placebo SQ every 4 weeks, n = 74 N = 218	• Omalizumab 300 mg: 45.2 • Omalizumab 150 mg: 39.4 • Placebo: 35.1 BMI (mean), kg/m^2: • Omalizumab 300 mg: 24.4 • Omalizumab 150 mg: 24.3 • Placebo: 23.3 Duration of disease state (mean), years: • Omalizumab 300 mg: 3.6 • Omalizumab 150 mg: 5.1 • Placebo: 4.7 DLQI[d] score (mean): • Omalizumab 300 mg: 12.0 • Omalizumab 150 mg: 11.0 • Placebo: 10.9 In-clinic UAS[a] (mean): • Omalizumab 300 mg: 5.1 • Omalizumab 150 mg: 5.2 • Placebo: 4.9 UAS7[b] (mean): • Omalizumab 300 mg: 31.8 • Omalizumab 150 mg: 29.6 • Placebo: 30.1 ISS7[c] (mean): • Omalizumab 300 mg: 14.6

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• Omalizumab 150 mg: 13.2 • Placebo: 13.7 Presence of angioedema (mean), %: • Omalizumab 300 mg: 12 • Omalizumab 150 mg: 12 • Placebo: 15 <u>Inclusion Criteria</u> • 12 to 75 years • CSU diagnosis ≥ 6 months and refractory to standard H_1-antihistamines at randomization • Itch and hives score ≥ 8 consecutive weeks • UAS7 ≥ 16; itch component ≥ 8 seven days prior to randomization • In-clinic UAS ≥ 4 • Approved H_1-antihistamines ≥ 3 consecutive days (immediately prior to day 14) <u>Exclusion Criteria</u> • Weight < 20 kg • Underlying cause for chronic urticaria or any skin disease with chronic itching not caused by CSU
Hide et al., 2018[17] NCT02329223 POLARIS	Randomized, double-blind, placebo-controlled, parallel-group multicenter phase 3: subgroup analysis Omalizumab SQ every 4 weeks • 150 mg, n = 34 • 300 mg, n = 35	Age (mean): 44.3 years Male (mean): 34.3% BMI (mean): 23.7 kg/m^2 Duration of CSU (mean): 4.8 years

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
	Placebo SQ every 4 weeks, n = 36 N = 105	In-clinic UAS[a] (mean): 5.0 UAS7[b] (mean): 29.6 ISS7[c] (mean): 13.2 Presence of angioedema (mean): 7.6% <u>Inclusion Criteria</u> • 12 to 75 years • CSU diagnosis ≥ 6 months and refractory to standard H_1-antihistamines at randomization • Itch and hives ≥ 8 consecutive weeks • UAS7 ≥ 16; itch component ≥ 8 seven days prior to randomization • In-clinic UAS ≥ 4 • Approved H_1-antihistamines ≥ 3 consecutive days (immediately prior to day 14) <u>Exclusion Criteria</u> • Weight < 20 kg • Underlying cause for chronic urticaria or any skin disease with chronic itching not caused by CSU
Casale et al., 2019[18] NCT02392624 XTEND-CIU Genentech High	Multicenter, randomized, double-blind, placebo-controlled Omalizumab 300 mg SQ every 4 weeks, n = 81 Placebo SQ every 4 weeks, n = 53 N = 134	Age (mean ± SD), years: • Omalizumab: 43.1 ± 14.7 • Placebo: 48.5 ± 13.2 Male (mean), %: • Omalizumab: 25.9 • Placebo: 24.5

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		White (mean), %: • Omalizumab: 84 • Placebo: 79.2 BMI (mean ± SD), kg/m^2: • Omalizumab: 29.8 ± 6.3 • Placebo: 30.8 ± 7.7 Duration of CIU symptoms (mean ± SD), months: • Omalizumab: 77.0 ± 118.8 • Placebo: 73.6± 67.3 Weekly number of hives (mean ± SD): • Omalizumab: 0.3 ± 0.7 • Placebo: 0.3 ± 0.8 ISS7[c] (mean ± SD): • Omalizumab: 0.4 ± 0.8 • Placebo: 0.5 ± 1.1 <u>Inclusion Criteria</u> • 12 to 75 years • Diagnosis of CIU refractory to H_1-antihistamines at ≥ 4 times approved dose • Presence of itch and hives ≥ 8 consecutive weeks • UAS7 ≥ 16; itch component ≥ 8 (7 days prior to baseline) • CIU diagnosis ≥ 6 months <u>Exclusion Criteria</u> • Omalizumab use within 30 days of screening • ≤ 20 kg

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• known cause of CIU other than CIU • parasitic infection • Underlying cause for chronic urticaria or any skin disease with chronic itching not caused by CIU • Pregnant or lactating women
Eosinophilic Granulomatosis With Polyangiitis		
Wechsler et al[5] NCT02020889 31 academic centers across 9 countries GlaxoSmithKline and National Institute of Allergy and Infectious Diseases (NIAID) Moderate	Randomized, placebo-controlled, double-blind, parallel-group, phase 3 Mepolizumab 300 mg SQ every 4 weeks, n = 68 Placebo SQ every 4 weeks, n = 68 Total, N = 136	Age (mean ± SD), years: • Mepolizumab: 49 ± 12 • Placebo: 48 ± 14 Male, %: • Mepolizumab: 38 • Placebo: 44 Prednisolone or prednisone dose, mg/day (median): • Mepolizumab: 12.0 • Placebo: 11.0 BVAS[g] > 0 (%): • Mepolizumab: 37 (54) • Placebo: 48 (71) Immunosuppressive therapy at baseline (%): • Mepolizumab: 41 (60) • Placebo: 31 (46) Asthma with eosinophilia diagnosis (%): • Mepolizumab: 68 (100) • Placebo: 68 (100) Relapsing disease (%):

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• Mepolizumab: 51 (75) • Placebo: 49 (72) Refractory disease (%): • Mepolizumab: 34 (50) • Placebo: 40 (59) Duration of diagnosis of EGPA, years: • Mepolizumab: 5.2 ± 4.4 • Placebo: 5.9 ± 4.9 <u>Inclusion Criteria</u> • ≥ 18 years old • Diagnosis of relapsing or refractory EGPA ≥ 6 months • Taking stable doses of prednisone or prednisolone (≥ 7.5 to ≤ 50 mg/day for ≥ 4 weeks with or without immunosuppressive therapy <u>Exclusion Criteria</u> • Diagnosis of granulomatosis with polyangiitis • Diagnosis of microscopic polyangiitis • Participants with organ threatening or life-threatening EGPA within 3 months
Hypereosinophilic Syndrome		
Rothenberg et al., 2008[6] NCT00086658 26 sites in United States, Canada, Belgium, France, Germany, Italy, Switzerland, and Australia	International, randomized, double-blind, placebo-controlled trial Mepolizumab group: 750 mg infused every 4 weeks, n = 43 Placebo: infused every 4 weeks, n = 42	Age (mean ± SD): 48.1 ± 15.3 years Male: 51% White: 85% Prednisone dose (%):

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
GlaxoSmithKline Moderate	Total, N = 85	• ≤ 30 mg/day: 71% • > 30 mg/day: 29% HES treatment ≤ 5 years: 95% Ongoing systemic corticosteroids treatment: 82% HES duration (mean ± SD): 5.4 ± 7.8 years Eosinophil count ($\times 10^{-9}$): 0.447 $\pm$ 0.694 <u>Inclusion Criteria</u> • Documented history of HES • Eosinophil count ≥ 1500 cells for 6 months • Signs and symptoms of organ system involvement • Stable prednisone dose prior to starting mepolizumab • Not pregnant/nursing <u>Exclusion Criteria</u> • Churg-Strauss Syndrome • Wegener's Granulomatosis • Lymphoma • Chemotherapy, radiotherapy or IL-2 treatment
Roufosse et al., 2020[7] NCT02836496 39 sites across 13 countries GlaxoSmithKline	Randomized, placebo-controlled, double-blind, parallel-group, multicenter, phase III trial Mepolizumab group: 300 mg SQ every 4 weeks, n = 54 Placebo: SQ every 4 weeks, n = 54	Age by group, mean (range): • Mepolizumab: 46.6 (12 to 82) • Placebo: 45.5 (15 to 80) Male by group, %: • Mepolizumab: 44 • Placebo: 50

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
Moderate	Total, N = 108	HES Duration by group, (mean± SD) years: • Mepolizumab: 5.6 ± 5.1 • Placebo: 5.7 ± 8.0 Baseline prednisone (or equivalent) therapy by group, %: Mepolizumab • ≤ 20 mg daily: 65 • > 20 mg daily: 69 Placebo • ≥ 20 mg daily: 9 • > 20 mg daily: 2 <u>Inclusion Criteria</u> • ≥ 12 years old • HES ≥ 6 months • 2+ HES flares within 12 months • Eosinophil count ≥ 1000 cells • Stable HES therapy ≥ 4 weeks • Not pregnant or breastfeeding <u>Exclusion Criteria</u> • Life-threatening HES • Preexisting, significant organ abnormalities not associated with HES • Liver or heart disease or abnormalities
Chronic Rhinosinusitis and Chronic Rhinosinusitis With Nasal Polyps		
Gevaert et al., 2020[24] NCT03280550 NCT03280537	Identical, randomized, double-blind, placebo-controlled, phase 3 trial Omalizumab group (Intranasal mometasone daily and 75 to 600	Age (mean with SD): POLYP 1: • Omalizumab: 50.0 ± 14.5 • Placebo: 52.2 ± 11.6 POLYP 2

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
POLYP 1 POLYP 2 82 sites in North America and Europe Genentech (Roche Group) and Novartis Pharmacy AG Moderate	mg SQ omalizumab every 2-4 weeks depending on pretreatment IgE and body weight), n = 134 Placebo group (Intranasal mometasone daily and matched placebo only), n = 131 Total, N = 265	• Omalizumab: 49.0 ± 11.9 • Placebo: 51.0 ± 12.0 Male: POLYP 1: • Omalizumab: 65.3% • Placebo: 62.1% POLYP 2 • Omalizumab: 62.9% • Placebo: 67.7% <u>Inclusion Criteria</u> • 18–75 years old with persistent bilateral nasal polyps, nasal congestion, and weight of 30–50 kg and serum IgE levels 30–1500 IU/mL • Received at least 4 weeks of intranasal corticosteroids before screening • NPS of ≥ 5 (≥ 2 for each nostril) at screening visit days 1 and 2 and after 4 weeks of intranasal mometasone • NCS ≥ 2 with postnasal drip, runny nose, and/or loss of sense of smell at screening day 1, and a weekly mean NCS >1 at randomization • SNOT-22 ≥ 20 at screening day 1 and randomization <u>Exclusion Criteria</u> • Current upper respiratory tract infection • Cystic fibrosis or other dyskinetic ciliary syndrome • Past or current malignancy • Cardiac condition • Hepatitis • Liver cirrhosis

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• Infection requiring hospitalization within the last 4 weeks • Antibiotic therapy within the last 2 weeks • Antifungal treatment • Parasitic infection within the last 6 months • Use of systemic corticosteroids within the last 2 months • Use of immunosuppressant, biologic, or leukotriene antagonist or modifier • Nasal surgery within the last 6 months • Immunocompromised • Known allergy to omalizumab
Pinto et al., 2010[28] NCT00117611 Single site in Chicago, IL, USA Genetech and McHugh Otolaryngology Research Fund Low	Randomized, double-blind, placebo-controlled clinical trial Omalizumab group ((.016 mg/kg per IU serum IgE/mL SQ every 2 or 4 weeks depending on patient weight), n = 7 Placebo group (matched placebo SQ every 4 weeks), n = 7 Total, N = 14	Age (mean ± SD): • 43.1 ± 9.8 (omalizumab) • 48.6 ± 9.1 (control) Male: 71.4% <u>Inclusion Criteria</u> • Age 18 – 75 years • Diagnosis of CRS • Serum total IgE 30 – 700 IU/mL <u>Exclusion Criteria</u> • Weight > 150 kg • Contraindications to omalizumab • Secondary causes of CRS including immunocompromised or genetic disease
Gevaert et al., 2013[23] University hospitals of Ghent and Leuven	Randomized, double-blind, placebo-controlled clinical study Omalizumab group (dose based on total serum IgE and body weight	Age (median, IQR): • Omalizumab: 50 (44 to 56) • Placebo: 45 (42 to 54) Male: 66.7%

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
Ghent University and Flemish Scientific Research Board Moderate	[max dose 375 mg] SQ every 2 or 4 weeks), n = 16 Placebo group (SQ every 4 weeks), n = 8 Total, N = 24	<u>Inclusion Criteria</u> • Age 18 years or older • Diagnosis of CRSwNP > 2 years • Diagnosis of asthma > 2 years • Total serum IgE 30 to 700 kU/mL
Bachert et al., 2019[10] NCT02912468 NCT02898454 LIBERTY NP SINUS-24 LIBERTY NP SINUS-52 SINUS-24: 67 hospitals/clinical centers in 13 countries (Bulgaria, Czechia, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Ukraine, Russia, United Kingdom, and United States) SINUS-52: 117 hospitals/clinical centers in 14 countries (Argentina, Australia, Belgium, Canada, Chile, Israel, Mexico, Portugal, Russia, Spain, Sweden, Turkey, Japan, and United States) Sanofi and Regeneron Pharmaceuticals	Multinational, randomized, double-blind, placebo-controlled, parallel-group studies SINUS-24 Dupilumab group (300 mg SQ dupilumab every 2 weeks), n = 143 Placebo group (matched placebo SQ every 2 weeks) n = 133 SINUS-52 Dupilumab group (300 mg SQ dupilumab every 2 weeks for 52 weeks), n = 150 Dupilumab group (300 mg SQ dupilumab every 2 weeks for 24 weeks, then every 4 weeks for 28 weeks), n =145 Placebo group (matched placebo SQ every 2 weeks), n = 153 Total, N = 724	Age (mean ± SD): SINUS-24 • Placebo: 50 ± 41.60 • Dupilumab: 52 ± 39.61 SINUS-52 • Placebo: 51 ± 42.61 • Dupilumab: 53 ± 42.63 Male: 60.4% <u>Inclusion Criteria</u> • Age 18 years or older • Bilateral nasal polyps • Symptoms of CRS refractory to intranasal corticosteroids • Received SCS in the previous 2 years, contraindication to SCS, or previous sino-nasal surgery • Bilateral NPS of ≥ 5 • NPS of ≥ 2 in each nostril • Have ≥ 2 symptoms (nasal congestion, nasal obstruction, loss of smell, rhinorrhea) <u>Exclusion Criteria</u> • FEV-1 ≤50% than predicted • Previous participation in dupilumab trial

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
Moderate		
Fujieda et al., 2021[26] NCT02898454 SINUS-52 Japanese study sites from the parent study Sanofi and Regeneron Pharmaceuticals Moderate	Subgroup analysis of a randomized, double-blind, placebo-controlled, parallel-group studies Dupilumab group A (300 mg SQ dupilumab every 2 weeks for 52 weeks), n = 150 Dupilumab group B (300 mg SQ dupilumab every 2 weeks for 24 weeks, then every 4 weeks for 28 weeks), n =145 Placebo group (matched placebo SQ every 2 weeks), n = 153 Total, N = 49	Age (mean ± SD): • Placebo: 55.9 ± 10.4 • Dupilumab group A: 50.5 ± 10.5 • Dupilumab group B: 54.1 ± 11.8 Male: 61.2% <u>Inclusion Criteria</u> • Age 18 years or older • Bilateral nasal polyps • Symptoms of CRS refractory to intranasal corticosteroids • Received SCS in the previous 2 years, contraindication to SCS, or previous sino-nasal surgery • Bilateral NPS of ≥ 5 • NPS of ≥ 2 in each nostril • Have ≥ 2 symptoms (nasal congestion, nasal obstruction, loss of smell, rhinorrhea) • Participant at a Japanese study center <u>Exclusion Criteria</u> • FEV-1 ≤50% than predicted • Previous participation in dupilumab trial
Maspero et al., 2020[27] NCT02414854 LIBERTY ASTHMA QUEST	*Post hoc* analysis of a phase 3, randomized, double-blinded, placebo-controlled study Dupilumab group (200 mg SQ every 2 weeks for 52 weeks), n = 631	Age (mean ± SD): CRS subgroup • Dupilumab 200 mg: 51.0 ± 10.6 • Dupilumab 300 mg: 52.7 ± 13.5 • Placebo 200 mg match: 52.3 ± 12.0 • Placebo 300 mg match: 49.6 ± 11.8

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
Sanofi Regeneron Pharmaceuticals Moderate	Dupilumab group (300 mg SQ every 2 weeks for 52 weeks), n = 633 Placebo group (matched placebo SQ every 2 weeks for 52 weeks), n = 638 Total, N = 1902	Non-CRS subgroup • Dupilumab 200 mg: 47.1 ± 16.2 • Dupilumab 300 mg: 46.5 ± 15.8 • Placebo 200 mg match: 47.2 ± 16.3 • Placebo 300 mg match: 15.4 ± 15.4 Male: 37% <u>Inclusion Criteria</u> • Age 12 years or older • Diagnosis of asthma for at least 1 year • Currently treated with medium to high dose of inhaled corticosteroid and a second controller therapy for ≥ 3 months with a stable dose for ≥ 1 month prior to first study visit • Prebronchodilator FEV-1 ≤ 80% predicted normal (adults) or ≤ 90% predicted normal (adolescents) at visits 1 and 2 • ACQ-5 score ≥ 1.5 at visits 1 and 2 • Reversibility of at least 12% and 200 mL in FEV-1 after bronchodilator • Within the last year: SCS use, hospitalization or emergency care for worsening asthma <u>Exclusion Criteria</u> • Age < 12 years or minimum legal age for adolescents in site country • Weight < 30 kg • Diagnosis of COPD or other lung disease that may impair lung function

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• Evidence of lung disease(s) other than asthma (clinical evidence or imaging) within 12 months of visit 1 • A severe asthma exacerbation at any time from 1 month before screening up to and including the baseline visit • Current smokers, or smokers who stopped within 6 months before screening or had a previous smoking history of > 10 pack-years • Biologic therapy/immunosuppressant within 2 months (or five half-lives) before screening • Exposure to another investigative antibody within five half-lives or 6 months before screening, or to any other (non-antibody) investigative agent within 30 days before screening • Comorbid disease that might interfere with the evaluation of dupilumab Previous treatment with dupilumab
Bachert et al., 2019[22] NCT01920893 13 sites in the United States and Europe (Belgium, Spain, Sweden) Sanofi and Regeneron Pharmaceuticals Moderate	Subgroup analysis of a randomized, double-blind, placebo-controlled parallel-group study Dupilumab group (600 mg loading dose followed by 300 mg SC weekly for 15 weeks), n = 30 Placebo group (matched placebo SC weekly for 15 weeks), n = 30 Total, N = 60	Age (mean ± SD): 48.4 ± 9.4 Male: 56.7% <u>Inclusion Criteria</u> • Age 18 to 65 years • Bilateral nasal polyposis • Chronis sinusitis refractory to intranasal corticosteroids for ≥ 2 months • Bilateral NPS ≥ 5 • NPS ≥ in each nostril • At least 2 of the following symptoms (nasal obstruction, rhinorrhea, facial pain or pressure, decreased sense of smell

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		Exclusion Criteria • Previous participation in dupilumab clinical trial • Received corticosteroids, monoclonal antibodies, immunosuppressive therapy, or anti-IgE therapy within 2 months • Previous nasal surgery within the last 6 months • History of ≥ 2 nasal polyp surgeries • Comorbid conditions interfering with ability to evaluate primary endpoint
Bachert et al., 2020[21] NCT01920893 13 sites in the United States and Europe (Belgium, Spain, Sweden) Sanofi and Regeneron Pharmaceuticals Moderate	Randomized, double-blind, placebo-controlled parallel-group study Dupilumab group (600 mg loading dose followed by 300 mg SC weekly for 15 weeks), n = 30 Placebo group (matched placebo SC weekly for 15 weeks), n = 30 Total, N = 60	Age (mean ± SD): 48.4 ± 9.4 Male: 56.7% Inclusion Criteria • Age 18 to 65 years • Bilateral nasal polyposis • Chronis sinusitis refractory to intranasal corticosteroids for ≥ 2 months • Bilateral NPS ≥ 5 • NPS ≥ in each nostril • At least 2 of the following symptoms (nasal obstruction, rhinorrhea, facial pain or pressure, decreased sense of smell Exclusion Criteria • Previous participation in dupilumab clinical trial • Received corticosteroids, monoclonal antibodies, immunosuppressive therapy, or anti-IgE therapy within 2 months • Previous nasal surgery within the last 6 months • History of ≥ 2 nasal polyp surgeries

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
		• Comorbid conditions interfering with ability to evaluate primary endpoint
Bachert et al., 2016[11] NCT01920893 13 sites in the United States and Europe (Belgium, Spain, Sweden) Sanofi and Regeneron Pharmaceuticals Moderate	Randomized, double-blind, placebo-controlled parallel-group study Dupilumab group (600 mg loading dose followed by 300 mg SC weekly for 15 weeks), n = 30 Placebo group (matched placebo SC weekly for 15 weeks), n = 30 Total, N = 60	Age (mean ± SD): 48.4 ± 9.4 Male: 56.7% <u>Inclusion Criteria</u> • Age 18 to 65 years • Bilateral nasal polyposis • Chronis sinusitis refractory to intranasal corticosteroids for ≥ 2 months • Bilateral NPS ≥ 5 • NPS ≥ in each nostril • At least 2 of the following symptoms (nasal obstruction, rhinorrhea, facial pain or pressure, decreased sense of smell <u>Exclusion Criteria</u> • Previous participation in dupilumab clinical trial • Received corticosteroids, monoclonal antibodies, immunosuppressive therapy, or anti-IgE therapy within 2 months • Previous nasal surgery within the last 6 months • History of ≥ 2 nasal polyp surgeries • Comorbid conditions interfering with ability to evaluate primary endpoint

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
Bachert et al., 2017[9] NCT01362244 Six centers in 3 countries (Belgium, Netherlands, United Kingdom) GlaxoSmithKline Moderate	Randomized, double-blind, placebo-controlled, study Mepolizumab group (Intranasal fluticasone daily and 750 mg mepolizumab via IV infusion every 4 weeks), n = 54 Placebo group (Daily intranasal fluticasone and matched placebo via IV infusion every 4 weeks), n = 53 Total, n = 107	Age (mean ± SD) • Mepolizumab: 51 ± 11 • Placebo: 50 ± 10 Male: 71.4% <u>Inclusion Criteria</u> • Age 18 to 70 years • Severe, recurrent, bilateral nasal polyps • Require nasal polyp surgery (NPS ≥ 3 in 1 nostril and ≥ 2 in the other • VAS nasal symptom score > 7 • Refractory to standard therapy (intranasal steroids and/or received oral steroids) • Previous history of nasal polyp surgery <u>Exclusion Criteria</u> • Continuous, high-dose oral steroid therapy • Treatment with other biologic agents within the previous 12 months • Asthma exacerbation requiring hospitalization within the last 4 weeks
Han et al., 2020[25] NCT03085797 SYNAPSE 93 centers in 11 countries (Argentina, Australia, Canada, Germany, the Netherlands, South Korea, Romania,	Randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial Mepolizumab group (standard of care plus 100 mg mepolizumab SQ every 4 weeks) n = 206	Age (mean ± SD): 48.8 ± 13.01 Male: 65% <u>Inclusion Criteria</u> • Age ≥ 18 years • Recurrent, refractory, severe, bilateral nasal polyp symptoms despite standard therapy • Eligible for repeat nasal surgery

Author, Year Clinical Trial Number Trial Name Sites Sponsor Risk of Bias	Study Design Drug and Comparator Dose or Frequency N Randomized	Demographic Characteristics Key Inclusion and Exclusion Criteria
Russia, Sweden, United Kingdom, United States GlaxoSmithKline Moderate	Placebo group (standard of care matched placebo SQ every 4 weeks) n = 201 Total, N = 407	• Previous history of nasal polyp surgery within the last 10 years • Stable maintenance therapy with mometasone intranasal spray for ≥ 8 weeks before screening • Two or more symptoms present for ≥ 12 weeks before screening
Gevaert et al., 2011[29] CRT110178 University Hospital in Ghent, Belgium Interuniversity Attraction Poles Programme, IST Programme of the European Community under the PASCAL2 Network of Excellence Moderate	Randomized, double-blind, placebo-controlled study Mepolizumab group (2 IV injections of 750 mg mepolizumab 28 days apart) n = 20 Placebo group (matched placebo) n = 10 Total, N = 30	Age (mean ± SD): • Mepolizumab: 50.05 ± 8.86 • Placebo: 45.9 ± 11.43 Male: 73.3% <u>Inclusion Criteria</u> • Diagnosis of CRSwNP • Failure of standard care for CRSwNP <u>Exclusion Criteria</u> • Use of SCS or surgical intervention from 1 month prior to study until 2 months after first dose

Abbreviations. AAS: Angioedema Activity Score; BVAS: Birmingham Vasculitis Activity Score; CIU: chronic idiopathic urticaria; CRS: chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyps; CSU: chronic spontaneous urticaria; CU: chronic urticaria; CU-Q_2oL: Chronic Urticaria Quality of Life; CVA: cerebrovascular accident; DLQI: Dermatology Life Quality Index; HES: Hypereosinophilic syndrome; IgE: Immunoglobulin E; IL-2: Interleukin-2; ISS7: Weekly Itch Severity Scale; IV: intravenously; LTRA: leukotriene receptor antagonist; NCS: Nasal Congestion Score; NPS: Nasal Polyp Score; SCS: systemic corticosteroids; SD: standard deviation; SNOT-22: Sino-nasal Outcome Test (22 questions); SQ: subcutaneous; TPO: thyroid peroxidase; UAS: Urticaria Activity Score; UAS7; Weekly Urticaria Activity Score; VAS: visual analog scale.

Table B2. Primary Outcomes, Secondary Outcomes, Additional Outcomes, and Follow-up

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
Chronic Spontaneous Urticaria				
Maurer et al., 2011[13]	After 24 weeks of treatment, change in mean UAS7[b] score from baseline	AUC over 24 weeks of UAS[a] Daily scores for: • Wheals • Pruritus • Erythema • Angioedema Concomitant medication use Global assessment, via Likert scale, of symptoms from both participants and investigators	Primary outcome Difference of UAS7[b] from baseline at 24 weeks • Omalizumab: −17.8 • Placebo: −7.9 Statistical significance between the 2 groups with a difference of 9.9 points in score (95% CI, 2.7 to 17.1; *P* < .01) Secondary outcomes • UAS[a] AUC lower in omalizumab group compared to placebo (*P* < .01) • Wheal score reduction significant for omalizumab vs. placebo (−9.2 vs. −3.3; *P* < .01) • Occurrence between omalizumab compared with placebo respectively: wheal development: 70.4% (19 of 27) vs. 4.5% (1 of 22) absence of pruritus: 59.3% (16 of 27) vs. 9.1% (2 of 22) absence of erythema: 66.7% (18 of 27) vs. 18.2% (4 of 22) absence of angioedema: 77.8% (21 of 27) vs. 36.4% (8 of 22)	27 weeks (3-week screening period and 24-week treatment period)
Maurer et al., 2013[2] NCT01292473 ASTERIA II	Change in ISS7[c] from baseline to 12 weeks	Change in baseline to week 12 for: • UAS7[b] • Weekly number of hives • Weekly size of the largest hive • DLQI[d] score	Primary outcome ISS7[c] change, mean ± SD • Placebo: −5.1 ± 5.6 • Omalizumab 75 mg: −5.9 ± 6.5 (−0.7, 95% CI, −2.5 to 1.2) • Omalizumab 150 mg: −8.1 ± 6.4 (−3.0, 95% CI, −4.9 to −1.2; *P* < .01) • Omalizumab 300 mg: −9.8 ± 6.0 (−4.8, 95% CI, −6.5 to −3.1; *P* < .01)	28 weeks (12-week treatment period and a 16-week follow up)

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
		MID of ISS7[c] by week 12; percentage of MID responders at week 12 Percentage UAS7[b] ≤ 6 at week 12 Percentage of angioedema-free days, week 4 to 12	<u>Secondary outcomes</u> Weekly number of hives change, mean ± SD • Placebo: −5.2 ± 6.6 • Omalizumab 75 mg: −7.2 ± 7.0 (−2.0, 95% CI, −4.1 to −0.1) • Omalizumab 150 mg: −9.8 ± 7.3 (−4.5, 95% CI, −6.7 to −2.4; *P* < .01) • Omalizumab 300 mg: −12.0 ± 7.6 (−7.1, 95% CI, −9.3 to −4.9; *P* < .01) UAS7[b] ≤ 6 at week 12 • Placebo: 19 % (15 of 79) • Omalizumab 75 mg: 27% (22 of 82) • Omalizumab 150 mg: 43% (35 of 82); *P* < .01 • Omalizumab 300 mg: 66% (52 of 79); *P* < .01 DLQI[d] score change, mean ± SD • Placebo: -6.1 ± 7.5 • Omalizumab 75 mg: 7.5 ± 7.2 (−1.7, 95% CI, −3.8 to 0.5) • Omalizumab 150 mg: −8.3 ± 6.3 (−2.5, 95% CI, −4.6 to −0.4; *P* = .02) • Omalizumab 300 mg: −10.2 ± 6.8 (−3.8, 95% CI, −5.9 to −1.7; *P* < .01) Angioedema-free days (week 4 to 12), mean ± SD • Placebo: 89.2 ± 19.0% • Omalizumab 75 mg: 93.5 ± 14.9% • Omalizumab 150 mg: 91.6 ± 17.4% • Omalizumab 300 mg: 95.5 ± 14.5%	
Kaplan et al., 2013[4] NCT01264939 GLACIAL	Evaluate the safety of omalizumab 300 mg compared to placebo via:		<u>Key efficacy endpoints</u>, mean Change in ISS7 from baseline to week 12: • Omalizumab: −8.6 (95% CI, −9.3 to −7.8; *P* < .01) • Placebo: −4.0 (95% CI, −5.3 to −2.7)	40 weeks (24-week treatment and a 16-

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
	• Incidence and severity of AEs and SAEs • Changes in vital signs • Clinical laboratory evaluations		Change in UAS7[b] at week 12 • Omalizumab: −19.0 (95% CI, −20.6 to −17.4; *P* < .01) • Placebo: 95% CI, −8.5 (−11.1 to −5.9) Weekly number of hives • Omalizumab: −10.5 (95% CI, −11.4 to −9.5; *P* < .01) • Placebo: 95% CI, −4.5 (−5.9 to −3.1) Change from baseline in weekly size of largest hive score at week 12 • Omalizumab: −8.8 (95% CI, −9.7 to −7.9; *P* < .01) • Placebo: −3.1 (95% CI, −4.3 to −1.9) DLQI[d] score • Omalizumab: −9.7 (95% CI, −10.6 to −8.8; *P* < .01) • Placebo: −5.1 (95% CI, −7.0 to −3.2) Percentage with UAS7[b] of ≤ 6 • Omalizumab: 52.4% (132 of 252); *P* < .01 • Placebo: 12.0 % (10 of 83) Percentage of change from baseline in mean ISS of ≥ 5 • Omalizumab: 69.8% (176 of 252); *P* < .01 • Placebo: 39.8% (33 of 83) Percentage of angioedema free days from weeks 4 to 12 • Omalizumab: 91% (95% CI, 88.2 to 93.8; *P* < .01) • Placebo: 88.1 (95% CI, 83.6 to 92.7) Time until MID achieved in ISS7[c], median (week) • Omalizumab: 2; *P* < .01 • Placebo: 5	week follow up)

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
Saini et al., 2015[1] NCT01287117 ASTERIA I	Change in ISS from baseline to week 12	• Change in UAS7[b] from baseline to week 12 • Time to MID in ISS7[c] • Participants with MID in ISS7[c] at week 12	<u>Primary outcome</u> Change in ISS7[c], mean ± SD • Omalizumab 300 mg: −9.4 ± 5.7 (−5.8; 95% CI, −7.5 to −4.1; *P* < .01) • Omalizumab 150 mg: −6.7 ± 6.3 (−3.0; 95% CI, −4.7 to −1.2; *P* < .01) • Omalizumab 75 mg: −6.5 ± 6.1 (−3.0; 95% CI, −4.7 to −1.2; *P* < .01) • Placebo: −3.6 ± 5.2 <u>Secondary outcomes</u> Change in UAS7[b], mean ± SD • Omalizumab 300 mg: −20.8 ± 12.2 (−12.8; 95% CI, −16.4 to −9.2; *P* <.01) • Omalizumab 150 mg: −14.4 ± 13.0 (−6.5; 95% CI, −10.3 to −2.8; *P* < .01) • Omalizumab 75 mg: −13.8 ± 13.3 (−5.8; 95% CI, −9.6 to 1.9; *P* < .01) • Placebo: −8.0 ± 11.5 Time to MID, median (weeks) • Omalizumab 300 mg: 1 (HR, 2.3; 95% CI, 1.6 to 3.4; *P* < .01) • Omalizumab 150 mg: 2 (HR, 1.5; 95% CI, 1.0 to 2.1; *P* = .03) • Omalizumab 75 mg: 3 (HR, 1.4; 95 CI, 1.0 to 2.0; *P* = .09) • Placebo: 4 Participants with MID, % • Omalizumab 300 mg: 75.3; *P* < .01 • Omalizumab 150 mg: 56.3; *P* = .02 • Omalizumab 75 mg: 55.8; *P* = .01 • Placebo: 36.6	40 weeks (24-week treatment and a 16-week follow up)

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
Staubach et al., 2016[3] Staubach et al., 2018[14] NCT01723072 X-ACT	Change in CU-Q_2oL[e] score from baseline to week 28	Angioedema-burdened days per week, n Number and size of angioedema episodes Time between consecutive angioedema episodes Disease activity via AAS Change in AE-QoL	<u>At end of follow-up</u> CU-Q_2oL[e] score, mean ± SD • Omalizumab: −23.9 ± 23; *P* < 0.1 • Placebo: −14.7 ± 19 AE-QoL[g], mean • Omalizumab: −41.4; *P* < .01 • Placebo: −24.2 DLQI[d] score, mean • Omalizumab: −10.5; *P* < .01 • Placebo: −5.6 Angioedema-burdened days, mean ± SD • Omalizumab: 14.6 ± 19.5; median, 9 days • Placebo: 49.5 ± 50.8; median, 30 days • AAS[f], mean ± SD • Omalizumab: −20.6 ± 21.5 (95% CI, −18.9 to −0.7; *P* = .04) • Placebo: −10.8 ± 21.3 UAS7[b], mean • Omalizumab: −16.8 ± 14.8 (95% CI, −16.2 to −3.9; *P* < .01) • Placebo: −6.5 ± 13.4	36 weeks (28-week treatment and 8-week follow-up)
Metz et al., 2017[15] NCT01599637	Change in the FceRI+ and/or IgE+ skin cells from baseline to week 12		Change from baseline to week 12: Omalizumab, n = 17 assessed Placebo, n = 8 assessed UAS7[b], itch component (mean ± SD) • Omalizumab: −11.4 ± 6.5; *P* = .01 • Placebo: −3.8 ± 6.6	20 weeks (12-week treatment and an 8-week follow up)

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			UAS7[b], hives component (mean ± SD) • Omalizumab: −11.6 ± 7.3; *P* = .02 • Placebo: −3.8 ± 7.7 Participants' global assessment of symptoms (mean ± SD) • Omalizumab: 0.9 ± 1.1; *P* = .03 • Placebo: 1.9 ± 1.0 Investigators global assessment of symptoms (mean ± SD) • Omalizumab: 0.8 ± 1.0; *P* = .02 • Placebo: 2.0 ± 1.3 DLQI[d] score ± SD (n = 16) • Omalizumab: 3.8 ± 6.6; *P* < .01 • Placebo: 14.6 ± 10.8 Skindex-29[h] score ± SD (n = 16) • Omalizumab: 6.2 ± 7.1; *P* < .01 • Placebo: 22.6 ± 10.3 CU-Q_2oL[e] score ± SD • Omalizumab: 14.5 ± 22.3; *P* < .01 • Placebo: 53.5 ± 29.8	
Hide et al., 2017[16] NCT02329223 POLARIS	Change in ISS7[c] score from baseline to week 12	Evaluated at week 12 • Change in UAS7[b] from baseline • Change in weekly hive score from baseline • Percentage with UAS7[b] ≤ 6 • Change in weekly size and largest	<u>Primary outcome</u> • Omalizumab 300 mg: −10.22 (−3.7; 95% CI, −5.3 to 2.1; *P* < .01) • Omalizumab 150 mg: −8.80 (−2.3; 95% CI, −3.9 to −0.7; *P* < .01) • Placebo: −6.51 <u>Secondary outcomes</u> Change from baseline in UAS7[b] • Omalizumab 300 mg: −22.4 (−8.6; 95% CI, −12.1 to −5.1; *P* < .01)	26 weeks (2-week screening, 12-week treatment, 12-week follow up

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
		hive score from baseline • Percentage of ISS7[c] MID • Percentage of complete responders, UAS7 = 0 • Change in DLQI[d] score from baseline	• Omalizumab 150 mg: −18.79 (−4.9; 95% CI, −8.5 to −1.3; *P* < .01) • Placebo: −13.9 Change in weekly hives from baseline • Omalizumab 300 mg: −12.17 (−4.8; 95% CI, −6.8 to −2.7; *P* < .01) • Omalizumab 150 mg: −10.04 (−2.6; 95% CI, −4.8 to −0.5; *P* = .02) • Placebo: −7.41 Percentage of responders, UAS7 ≤ 6 (%) • Omalizumab 300 mg: 57.5 (OR, 7.6; 95% CI, 3.4 to 16.8; *P* < .01) • Omalizumab 150 mg: 42.9 (OR, 3.4; 95% CI, 1.6 to 7.5; *P* < .01) • Placebo: 18.9 Percentage with ISS7[c] MID (%) • Omalizumab 300 mg: 87.7 (OR, 5.5; 95% CI, 2.4 to 12.9; *P* < .01) • Omalizumab 150 mg: 68.6 (OR, 1.8; 95% CI, 0.9 to 3.7; *P* = .09) • Placebo: 55.4 Percentage of complete responders, UAS7 = 0 (%) • Omalizumab 300 mg: 35.6 (OR, 15.3; 95% CI, 4.3 to 54.9; *P* < .01) • Omalizumab 150 mg: 18.6 (OR, 5.4; 95% CI, 1.4 to 20.1; *P* < .01) • Placebo: 4.1 Change in DLQI[d] score from baseline • Omalizumab 300 mg: −8.4	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			(−3.1; 95% CI, −4.6 to −1.7; *P* < .01) • Omalizumab 150 mg: −7.2 (−1.9; 95% CI, −3.4 to −0.4; *P* = .01) • Placebo: −5.3	
Hide et al., 2018[17] NCT02329223 POLARIS	Change in ISS7[c] score from baseline to week 12	Evaluated at week 12 • Change in UAS7[b] from baseline • Change in weekly hive score from baseline • Percentage with UAS7[b] ≤ 6 • Change in weekly size and largest hive score from baseline • Percentage of ISS7[c] MID • Percentage of complete responders • Change in DLQI[d] score from baseline	<u>Primary outcome</u> • Omalizumab 300 mg: −9.54 (−4.4; 95% CI, −6.8 to −2.0) • Omalizumab 150 mg: −7.29 (−2.1; 95% CI, −4.5 to 0.3) • Placebo: −5.17 <u>Secondary outcome</u> Change from baseline in UAS7[b] • Omalizumab 300 mg: −21.61 (−10.7; 95% CI, −16.0 to −5.5) • Omalizumab 150 mg: −15.59 (−4.7; 95% CI, −10.0 to 0.6) • Placebo: −10.88 Change in weekly hive score from baseline • Omalizumab 300 mg: −12.06 (−6.3; 95% CI, −9.4 to −3.2) • Omalizumab 150 mg: −8.36 (−2.6; 95% CI, −5.7 to 0.6) • Placebo: −5.77 Percentage of responders, UAS7 ≤ 6 (%) • Omalizumab 300 mg: 54.3 (19 of 35) • Omalizumab 150 mg: 35.3 (12 of 34) • Placebo: 16.7 (6 of 36) Percentage with ISS7[c] MID (%) • Omalizumab 300 mg: 85.7 (30 of 35) • Omalizumab 150 mg: 64.7 (22 of 34)	26 weeks (2-week screening, 12-week treatment, 12-week follow up

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• Placebo: 52.8 (19 of 36) Percentage of complete responders, USA = 0 (%) • Omalizumab 300 mg: 31.4 (11 of 35) • Omalizumab 150 mg: 11.8 (4 of 34) • Placebo: 2.8 (1 of 36) Change in DLQI[d] score from baseline • Omalizumab 300 mg: −6.7 (−3.6; 95% CI, −5.2 to −1.9) • Omalizumab 150 mg: −5.7 (2.6; 95% CI, −4.3 to −1.0) • Placebo: −3.1	
Casale et al., 2019[18] NCT02392624 XTEND-CIU	Percentage of participants experiencing clinical worsening of CIU determined by UAS7[b] score ≥ 12 at least ≥ 2 consecutive weeks	• Time to clinical worsening of CIU by UAS7[b] • Change of UAS7[b] from randomization (week 24) to week 48 • Retreatment efficacy	*End of 24-week open-label phase: omalizumab* Moderate clinical insomnia (ISI), mean ± SD • Baseline: 15.8 ± 6.9 • Week 24: 4.5 ± 5.8 Mild anxiety (GAD-7), mean ± SD: • Baseline: 7.6 ± 6.3 • Week 24: 2.9 ± 3.8 DLQI[d] score, mean ± SD • Baseline: 14.8 ± 6.9 • Week 24: 2.2 ± 4.4 U-AIM score, mean ± SD • Baseline: 35.8 ± 6.7 • Week 24: 8.2 ± 11.3 UCT • Baseline: 2.5 ± 2.5 • Week 24: 13.6 ± 3.8	60 weeks (24-week open label, 24-week double-blind treatment, and 12-week follow up)

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			<u>*End of 24-week double-blind phase*</u> DLQI[d] score • Omalizumab: 66% (95% CI, 51.7% to 78.5%; *P* < .01) • Placebo: 19.8% (95% CI, 11.7% to 30.1%) Percentage of clinical worsening (UAS7[b]) • Omalizumab: 21% (95% CI, 12.7% to 32.5%; *P* < .01) • Placebo: 60.4% (95% CI, 46% to 73.5%)	
Eosinophilic Granulomatosis With Polyangiitis				
Wechsler et al., 2017[5] NCT02020889	Total accrued weeks of remission[i] • 0 wk • > 0 to < 12 wks • 12 to < 24 wks • 24 to < 36 wks • >36 wks • Proportion with remission[i] at both week 36 and week 48	• Remission[i] in first 24-weeks of trial that remains until end of treatment period • First EGPA relapse[j] • Proportion with prednisone or prednisolone doses of: 0 mg daily 0 mg to 4 mg daily > 4 mg to < 7.5 mg daily ≥ 7.5 mg daily	<u>Primary outcome</u> Total accrued weeks of remission[i] over 52 weeks • Mepolizumab, (%) 24 to < 36 wks: 10 (15); ≥ 36 wks: 13 (9 of 68) • Placebo, (%) 24 to < 36 wks: 0; ≥36 wks: 3 (2 of 68) (OR, 5.91; 95% CI, 2.7 to 13.0; *P* < .01) *OR determined for accrued remission of ≥24 weeks* Remission[i] at week 36 and week 48, (%) • Mepolizumab: 32 (22 of 68) • Placebo: 3 (2 of 68) (HR, 16.7; 95% CI, 3.6 to 77.6; *P* < .01) <u>Secondary outcomes</u> Remission[i] sustained from week 24 to 52, (%) • Mepolizumab: 19 (13 of 68) • Placebo: 1 (1 of 68) (HR, 19.7; 95% CI, 2.3 to 167.9; *P* < .01) First EGPA relapse[j], (%) • Mepolizumab: 56 (38 of 68)	60 weeks (52-week treatment period; 8-week follow up period)

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• Placebo: 82 (56 of 68) (HR, 0.3; 95% CI, 0.2 to 0.5; *P* < .01)	
Hypereosinophilic Syndrome				
Rothenberg et al., 2008[6] NCT00086658	Reduction in daily prednisone dose (≤ 10 mg for > 8 consecutive weeks)	Blood eosinophil count < 600 µL for ≥ 8 weeks Time to treatment failure Prednisone dose of ≤ 7.5 mg daily for ≥ 1 day No prednisone dose for ≥ 1 day Average daily prednisone dose at week 36 Daily prednisone dose of ≤ 10 mg by week 20 for ≥ 8 consecutive weeks	<u>Primary outcome</u> • Mepolizumab: *All participants*: 84% (36 of 43) (HR, 2.90; 95% CI, 1.6 to 5.3; *P* < .01) *≤ 30 mg prednisone at baseline*: 87% (26 of 30) (HR, 2.39; 95% CI, 1.3 to 4.5; *P* < .01) *> 30 mg prednisone at baseline*: 77% (10 of 13) (RR, 9.2; 95% CI 1.4 to 61.7; *P* < .01) • Placebo: *All patients*: 43% (18 of 42) *≤ 30 mg prednisone at baseline*: 57% (17 of 30) *> 30 mg prednisone at baseline*: 8% (1 of 12) <u>Secondary outcomes</u> Blood eosinophil count < 600 µL for ≥ 8 weeks • Mepolizumab: *All participants*: 95% (41 of 43) (HR, 3.53; 95% CI, 1.9 to 6.5; *P* < .01) *≤ 30 mg prednisone at baseline*: 93% (28 of 30) (HR, 2.3; 95% CI, 1.2 to 4.3; *P* < .01) *> 30 mg prednisone at baseline*: 100% (13 of 13) (RR, 12; 95% CI, 1.8 to 78.4; *P* < .01) • Placebo: *All patients*: 45% (19 of 42) *≤ 30 mg prednisone at baseline*: 60% (18 of 30) > 30 mg prednisone at baseline: 8% (1 of 12) Prednisone dose of ≤ 7.5 mg daily for ≥ 1 day • Mepolizumab: 86% (37 of 43) (HR, 2.7; 95% CI, 1.6 to 4.7; *P* < .01)	Efficacy: 36 weeks Safety: 48 weeks

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• Placebo: 50% (21 of 42) No prednisone dose for ≥ 1 day • Mepolizumab: 79% (34 of 43) (HR, 3.6; 95% CI, 1.8 to 7.3; *P* < .01) • Placebo: 24% (10 of 42)	
Roufosse et al., 2020[7] NCT02836496	Proportion of those with a flare occurrence during study period	Time to first flare Proportion with flare during weeks 20 to 32 Annual rate of flares Fatigue severity	<u>Primary outcome</u> • Mepolizumab: 28% (15 of 54) • Placebo: 56% (30 of 54) (OR, 0.28; 95% CI, 0.1 to 0.6) <u>Secondary outcomes</u> Time to first flare • Mepolizumab: 26.3% (95% CI, 16.5 to 40.3) • Placebo: 52.7% (95% CI, 40.1 to 66.5) • HR: 0.34 (0.18 to 0.67) Proportion with flare during weeks 20 to 32 • Mepolizumab: 13% (7 of 54) • Placebo: 31% (17 of 54) Annual rate of flares (mean) • Mepolizumab: 0.50 • Placebo: 1.46 (RR, 0.34; 95% CI, 0.19 to 0.63; *P* < .01) Fatigue severity change (median) • Mepolizumab: −0.66; *P* = .04 • Placebo: 0.32	Efficacy: 32 weeks Up to 40 weeks

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
Chronic Rhinosinusitis and Chronic Rhinosinusitis With Nasal Polyps				
Gevaert et al., 2020[24] POLYP 1: NCT03280550 POLYP 2: NCT03280537	Change from baseline to week 24 in endoscopic NPS Mean daily NCS	Change in baseline at week 24 in SNOT-22 score, UPSIT score, mean daily sense of smell, postnasal drip, runny nose, and TNSS Change from baseline at week 16 in NPS and NCS Percentage of patients requiring systemic corticosteroids for ≥ 3 consecutive days and/or nasal polypectomy by week 24 Percentage of patients with asthma demonstrating an MCID in improvement ≥ 0.5 points in AQLQ score through week 24 Percentage of patients in pooled population achieving ≥ 2-point	<u>Change in NPS at week 24</u> POLYP 1 omalizumab (n = 72) vs. placebo (n = 66) Adjusted mean NPS change (SE) • Change of −1.08 (0.16) vs. 0.06 (0.16) • Treatment difference −1.14 (95% CI, −1.59 to −0.69; *P* < .001) POLYP 2 omalizumab (n = 62) vs. placebo (n = 65) Adjusted mean NPS change (SE) • Change of −0.90 (0.17) vs. −0.31 (0.16) • Treatment difference −0.59 (95% CI, −1.05 to −0.12; *P* = .014) Pooled results • ≥ 1 point improvement 56.3% vs. 28.7% placebo • ≥ 2 point improvement 31.3% vs. 11.6% placebo Change in NCS at week 24 POLYP 1 omalizumab (n = 72) vs. placebo (n = 66) Adjusted mean NCS change (SE) • Change of −0.89 (0.10) vs. −0.35 (0.11) • Treatment difference −0.55 (95% CI, −0.84 to −0.25; *P* < .001) POLYP 2 omalizumab (n = 62) vs. placebo (n = 65) Adjusted mean NCS change (SE) • Change of −0.70 (0.11) vs. −0.20 (0.11) • Treatment difference −0.50 (95% CI, −0.80 to −0.19; *P* = .002) Pooled Results • ≥ 1 point improvement 44.4% vs. 21.4% placebo	24 weeks 28 weeks (safety)

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
		or at a least 1-point improvement in NPS and at least a 1-point improvement in NCS	<u>Change in NPS at week 16</u> POLYP 1 omalizumab (n = 72) vs. placebo (n = 66) Adjusted mean NPS change (SE) • Change of −0.98 (0.14) vs. 0.03 (0.15) • Treatment difference −1.01 (95% CI, −1.43 to −0.60; *P* < .001) POLYP 2 omalizumab (n = 62) vs. placebo (n = 65) Adjusted mean NPS change (SE) • Change of −1.20 (0.17) vs. −0.29 (0.16) • Treatment difference −0.91 (95% CI, −1.39 to −0.44; *P* < .001) <u>Change in NCS at week 16</u> POLYP 1 omalizumab (n = 72) vs. placebo (n = 66) Adjusted mean NCS change (SE) • Change of −0.89 (0.09) vs. −0.32 (0.10) • Treatment difference −0.57 (95% CI, −0.83 to −0.31; *P* < .001) POLYP 2 omalizumab (n = 62) vs. placebo (n = 65) Adjusted mean NCS change (SE) • Change of −0.80 (0.10) vs. −0.21 (0.10) • Treatment difference −0.59 (95% CI, −0.87 to −0.30; *P* < .001) <u>SNOT-22 score</u> Change at week 16 POLYP 1 omalizumab (n = 72) vs. placebo (n = 66) Adjusted mean change (SE) • Change of −24.70 (2.01) vs. −8.58 (2.01) • Treatment difference −16.12 (95% CI, −21.86 to −10.38; *P* < .001)	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			POLYP 2 omalizumab (n = 62) vs. placebo (n = 65) Adjusted mean change (SE) • Change of −21.59 (2.25) vs. −6.55 (2.19) • Treatment difference −15.04 (95% CI, −21.26 to −8.82; *P* < .001) <u>UPSIT score</u> Change at week 24 POLYP 1 omalizumab (n = 72) vs. placebo (n = 66) Adjusted mean change (SE) • Change of 4.44 (0.84) vs. 0.63 (0.90) • Treatment difference −3.81 (95% CI, 1.38 to −6.24; *P* = .002) POLYP 2 omalizumab (n = 62) vs. placebo (n = 65) Adjusted mean change (SE) • Change of −4.31 (0.83) vs. 0.44 (0.81) • Treatment difference −3.86 (95% CI, 1.57 to 6.15; *P* = .001) <u>TNSS</u> Change at week 24 POLYP 1 omalizumab (n = 72) vs. placebo (n = 66) Adjusted mean change (SE) • Change of −2.97 (0.33) vs. −1.06 (0.34) • Treatment difference −1.91 (95% CI, −2.85 to −0.96; *P* < .001) POLYP 2 omalizumab (n = 62) vs. placebo (n = 65) Adjusted mean change (SE) • Change of −2.53 (0.33) vs. −0.44 (0.32) • Treatment difference −2.09 (95% CI, −3.00 to −1.18; *P* < .001)	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			<u>Individual nasal symptoms</u> Loss of smell POLYP 1 omalizumab (n = 72) vs. placebo (n = 66) Adjusted mean change (SE) • Change of −0.56 (−0.09) vs. −0.23 (0.10) • Treatment difference −0.33 (95% CI, −0.60 to −0.06; *P* < .001) POLYP 2 omalizumab (n = 62) vs. placebo (n = 65) Adjusted mean change (SE) • Change of −0.58 (0.10) vs. −0.13 (0.10) • Treatment difference −0.45 (95% CI, −0.73 to −0.16; *P* = .002) Postnasal Drip POLYP 1 omalizumab (n = 72) vs. placebo (n = 66) Adjusted mean change (SE) • Change of −0.72 (−0.10) vs. −0.16 (0.10) • Treatment difference −0.56 (95% CI, −0.84 to −0.28; *P* < .001) POLYP 2 omalizumab (n = 62) vs. placebo (n = 65) Adjusted mean change (SE) • Change of −0.55 (0.10) vs. 0 (0.10) • Treatment difference −0.54 (95% CI, −0.81 to −0.27; *P* < .001) Runny nose score POLYP 1 omalizumab (n = 72) vs. placebo (n = 66) Adjusted mean change (SE) • Change of −0.77 (−0.10) vs. −0.34 (0.10) • Treatment difference −0.43 (95% CI, −0.70 to −0.16; *P* = .002) POLYP 2 omalizumab (n = 62) vs. placebo (n = 65) Adjusted mean change (SE)	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• Change of −0.70 (0.10) vs. −0.08 (0.10) • Treatment difference −0.63 (95% CI, −0.90 to −0.35; *P* < .001) Odds of achieving ≥ 0.5 points improvement in AQLQ score • POLYP 1: 3.7 • POLYP 2: 4.0 Rescue SCS use omalizumab (n = 129) vs. placebo (n = 129) • SCS use in 2.3% vs. 6.2% • Nonsignificant 62.5% relative reduction • 3.9% absolute difference Reduced need for surgery by week 24 POLYP 1 omalizumab (n = 69) vs. placebo (n = 65) • Reduction: 18.8% vs. 3.1% • OR: 6.3 (95% CI, 1.3 to 29.6) POLYP 2 omalizumab (n = 59) vs. placebo (n = 63) • Reduction: 16.9% vs. 3.2%) • OR: 6.2 (95% CI, 1.2 to 60.2) No sinus surgeries or polypectomies were recorded	
Pinto et al., 2010 [28] NCT00117611	Sinus inflammation, as determined by CT imaging compared pretreatment and posttreatment	Quality of life: SF-36, SNOT-20 Nasal airflow: NPIF Olfactory function: UPSIT Symptoms, nasal endoscopy scores, eosinophil counts in the nasal lavage	Sinus inflammation • Omalizumab (n = 7) 60.0% at 6 months vs. 76.1% at baseline (*P* < .043) • Placebo (n = 6) 66.1% vs. 75.9% (nonsignificant; *P* < .463) • No significant difference in magnitude of change <u>SNOT-20</u> • Clinically significant (−1.05) change in median SNOT-20 score for omalizumab (n = 7) vs. nonsignificant change (−0.20) in placebo (n = 7) <u>SF-36</u>	6 months

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• No significant differences within treatments in SF-36 • Significant difference in SF-36 vitality domain ($P < .05$) for omalizumab (9.4) vs. placebo (12.5) <u>UPSIT</u> • No significant differences in score change ($P < 0.31$) <u>Nasal endoscopy score</u> • No significant differences in score change • Nonsignificant net change in omalizumab (0) vs. placebo (−0.5; $P < .58$) Eosinophils in nasal lavage • No significant differences ($P > .05$) NPIF • No significant differences ($P > .05$) <u>TNSS</u> • No significant differences ($P > .05$) • No significant net difference across groups ($P < .21$) Reduced SCS use • Omalizumab (median = 0) vs. placebo (median = 1; $P < .043$) Trend toward decreased antibiotic use in omalizumab (median 0) vs. placebo (median = 1; $P < 0.32$)	
Gevaert et al., 2013[23]	Reduction in TPS after 16 weeks	Changes in Lund-Mackay CT scores Nasal symptoms: RSOM-31 Asthma symptoms Spirometry	<u>Difference in TPS at 16 weeks</u> • Significant decrease in polyp size compared to baseline in omalizumab group (−2.67; $P = .001$) • No significant decrease in poly size compared to baseline in placebo group (−0.12; $P = .99$)	16 weeks

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
		Quality of life: SF-36, AQLQ	TPS • Significantly lower in omalizumab group vs. placebo at all time points (*P* = .02) Lund-Mackay CT score changes at 16 weeks • Significant improvement in omalizumab group (*P* = .02) • Significant worsening in placebo group (*P* = .10) • Significant improvement in the omalizumab group compared to placebo (*P* = .04) Symptom scores • Improved nasal congestion (*P* = .002) • Improved anterior rhinorrhea (*P* = .003) • Improved loss sense of smell (*P* = .004) • Improved wheeze (*P* = .02) • Improved dyspnea (*P* = .02) • Nonsignificant improvement in cough and spirometry <u>SF-36</u> • Physical health domain significantly improved (*P* = .02) in omalizumab but not placebo (*P* = .75) • Mental health did not significantly improve in either group <u>RSOM-31</u> • Sleep significantly improved (*P* = .003) in omalizumab but not placebo • General symptoms significantly improved (*P* = .01) in omalizumab but not placebo <u>AQLQ</u> • Significant improvement (0.81) in the omalizumab group (*P* = .003) • Nonsignificant improvement (0.27) in the placebo group	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• Significant improvement (*P* = .002) in activity limitations domain for omalizumab • Significant improvement (*P* = .01) in symptom domain for omalizumab • Significant improvement (*P* = .02) in emotional function domain for omalizumab • Total score improvement in nonallergic (n = 8) participants (−59.4; *P* = .03) • Nonsignificant change in allergic (n = 7) participants (−12.3; *P* = .12)	
Bachert et al., 2019[10] NCT02912468 NCT02898454 LIBERTY NP SINUS-24 LIBERTY NP SINUS-52	Change from baseline in NPS at 24 weeks Change baseline in NCS at 24 weeks	Change from baseline at 24 weeks Lund-Mackay CT score Total symptom score Daily loss of smell or smell impairment SNOT-22 score UPSIT score FEV-1 ACQ-6 Change from baseline at 52 weeks NPS Nasal congestion SNOT-22 score Proportion of patients requiring	<u>Bilateral NPS at 24 weeks</u> SINUS-24 dupilumab (n = 143) vs. placebo (n = 133) • LS mean difference: −2.06 (95% CI, −2.43 to −1.69; *P* < .001) SINUS-52 dupilumab q2w (n = 295) vs. placebo (n = 153) • LS mean difference: −1.80 (95% CI, −2.10 to −1.51; *P* < .001) <u>NCS at 24 weeks</u> SINUS-24 dupilumab (n = 143) vs. placebo (n = 133) • LS mean difference: −0.89 (95% CI, −1.07 to −0.71; *P* < .001) • SINUS-52 dupilumab q2w (n = 295) vs. placebo (n = 153) • LS mean difference: −0.87 (95% CI, −1.03 to −0.71; *P* < .001) <u>Lund-Mackay CT score at 24 weeks</u> SINUS-24 dupilumab (n = 143) vs. placebo (n = 133) • LS mean difference: −7.44 (95% CI, −8.35 to −6.53; *P* < .001) SINUS-52 dupilumab (n = 295) vs. placebo (n = 153) • LS mean difference: −5.13 (95% CI, −5.80 to −4.46; *P* < .001)	SINUS-24 • Treatment phase: 24 weeks • Follow-up phase: 24 weeks SINUS-52 • Treatment phase: 52 weeks • Follow-up phase: 12 weeks

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
		SCS or need for sino-nasal surgery Proportion of participants with ≥ 1 point or ≥ point improvement in NPS Change from baseline in rhinosinusitis disease severity (VAS) PNIF	<u>Total Symptom Score at 24 weeks</u> SINUS-24 dupilumab (n = 143) vs. placebo (n = 133) • LS mean difference: −2.61 (95% CI, −3.04 to −2.17; *P* < .001) SINUS-52 dupilumab (n = 295) vs. placebo (n = 153) • LS mean difference: −2.44 (95% CI, −2.87 to −2.02; *P* < .001) <u>UPSIT Score at 24 weeks</u> SINUS-24 dupilumab (n = 143) vs. placebo (n = 133) • LS mean difference: 10.56 (95% CI, 8.79 to 12.34; *P* < .001) SINUS-52 dupilumab (n = 295) vs. placebo (n = 153) • LS mean difference: 10.52 (95% CI, 8.98 to 12.07; *P* < .001) <u>Loss of Smell Score at 24 weeks</u> SINUS-24 dupilumab (n = 143) vs. placebo (n = 133) • LS mean difference: −1.12 (95% CI, −1.31 to −0.93; *P* < .001) SINUS-52 dupilumab (n = 295) vs. placebo (n = 153) • LS mean difference: −0.98 (95% CI, −1.15 to −0.81; *P* < .001) <u>SNOT-22 Score at 24 weeks</u> SINUS-24 dupilumab (n = 143) vs. placebo (n = 133) • LS mean difference: −21.12 (95% CI, −25.17 to −17.06; *P* < .001) SINUS-52 dupilumab (n = 295) vs. placebo (n = 153) • LS mean difference: −17.36 (95% CI, −20.87 to −13.85; *P* < .001) <u>Bilateral NPS at 52 weeks</u> SINUS-52 dupilumab (n = 295) vs. placebo (n = 153)	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• LS mean difference: −2.40 (95% CI, −2.77 to −2.02; *P* < .001) <u>≥ 2-point NPS improvement</u> • Dupilumab (24 weeks) vs. matched placebo: 46% vs. 5% • Dupilumab (52 weeks) vs. matched placebo: 46% vs. 1% <u>NCS at 52 weeks</u> SINUS-52 dupilumab (n = 295) vs. placebo (n = 153) • LS mean difference: −0.98 (95% CI, −1.17 to −0.79; *P* < .001) <u>SNOT-22 Score at 52 weeks</u> SINUS-52 dupilumab (n = 295) vs. placebo (n = 153) • LS mean difference: −20.96 (95% CI, −25.03 to −16.89; *P* < .001) <u>FEV-1:</u> Dupilumab-24 weeks (n = 438) vs. placebo (n = 286) • LS mean difference: 0.21 (95% CI, 0.13 to 0.29; *P* < .001) <u>ACQ-6:</u> Dupilumab-24 weeks (n = 438) vs. placebo (n = 286) • LS mean difference: −0.82 (95% CI, −0.98 to −0.67; *P* < .001) Patients requiring SCS or nasal polyp surgery Dupilumab-24 weeks (n = 438) vs. placebo (n = 286) • 10% vs. 34% • HR: 0.243 (95% CI, 0.169 to 0.351; *P* < .001)	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
Fujieda et al., 2021[26] NCT02898454 SINUS-52	Change from baseline in NPS at 24 weeks Change from baseline in NCS at 24 weeks Change from baseline in Lund-Mackay CT score at 24 weeks	Change in SNOT-22 and UPSIT at 24 weeks Change from baseline in NPS, NCS, and SNOT-22 at 52 weeks Time to first SCS use and/or surgery	<u>NPS Score at 24 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −3.1 (95% CI, −4.3 to −1.8; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −2.1 (95% CI, −3.4 to −0.8; *P* = .001) <u>NPS Score at 52 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −3.5 (95% CI, −4.8 to −2.3; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −2.4 (95% CI, −3.7 to −1.1; *P* < .001) <u>NCS Score at 24 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −1.2 (95% CI, −1.7 to −0.7; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −0.9 (95% CI, −1.4 to −0.5; *P* < .001) <u>NCS Score at 52 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −1.2 (95% CI, −1.7 to −0.7; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −0.9 (95% CI, −1.4 to −0.4; *P* < .001) <u>Total Symptom Score at 24 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −3.4 (95% CI, −4.5 to −2.4; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −2.5 (95% CI, −3.6 to −1.4; *P* < .001) <u>Total Symptom Score at 52 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −4.0 (95% CI, −5.3 to −2.6; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16)	Treatment phase: 52 weeks Follow-up phase: 12 weeks

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• LS mean difference: −2.8 (95% CI, −4.1 to −1.5; *P* < .001) <u>Loss of Smell Score at 24 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −1.5 (95% CI, −2.0 to −1.0; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −0.9 (95% CI, −1.5 to −0.4; *P* < .001) <u>Loss of Smell Score at 52 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −1.8 (95% CI, −2.4 to −1.1; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −1.1 (95% CI, −1.7 to −0.5; *P* < .001) <u>UPSIT Score at 24 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: 12.7 (95% CI, 7.5 to 17.9; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: 7.6 (95% CI, 2.4 to 12.7; *P* = .004) <u>UPSIT Score at 52 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: 12.7 (95% CI, 7.8 to 17.7; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: 8.5 (95% CI, 3.6 to 13.4; *P* < .001) <u>SNOT-22 Score at 24 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −16.1 (95% CI, −25.8 to −6.5; *P* = .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −11.4 (95% CI, −20.8 to −1.9; *P* = .019)	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			<u>SNOT-22 Score at 52 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −18.9 (95% CI, −29.1 to −8.8; *P* = .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −11.5 (95% CI, −21.4 to −1.6; *P* = .023) <u>VAS for rhinosinusitis at 24 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −4.2 (95% CI, −6.1 to −2.3; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −2.7 (95% CI, −4.7 to −0.8; *P* = .005) <u>VAS for rhinosinusitis at 52 weeks</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −5.2 (95% CI, −7.5 to −3.0; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −3.0 (95% CI, −5.2 to −0.8; *P* = .008) <u>ACQ-6:</u> Dupilumab (n = 33) vs. placebo (n = 16) • LS mean difference: −1.45 (95% CI, −2.09 to −0.82; *P* < .001) <u>FEV-1:</u> Dupilumab (n = 33) vs. placebo (n = 16) • LS mean difference: 0.34 (95% CI, 0.05 to 0.63; *P* = .023) <u>Lund-Mackay CT Score at 24 weeks:</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −5.1 (95% CI, −8.2 to −2.0; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −2.8 (95% CI, −5.9 to −0.3; *P* = .042)	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			<u>Lund-Mackay CT Score at 52 weeks:</u> Dupilumab q2w (n = 16) vs. placebo (n = 16) • LS mean difference: −7.5 (95% CI, −10.9 to −4.0; *P* < .001) Dupilumab q2w-q4w (n = 17) vs. placebo (n = 16) • LS mean difference: −3.6 (95% CI, −7.1 to −0.2; *P* = .037)	
Maspero et al., 2020[27] NCT02414854 LIBERTY ASTHMA QUEST	Annualized severe asthma exacerbation rate Change from baseline in prebronchodilator and postbronchodilator FEV-1	ACQ-5 AQLQ SNOT-22 Biomarkers of inflammation	<u>Prebronchodilator FEV-1</u> CRS subgroup Dupilumab 200 mg vs. placebo • LS mean difference: 0.2 (95% CI, 0.10 to 0.31; *P* < .001) at week 2 • LS mean difference: 0.18 (95% CI, 0.06 to 0.30; *P* = .004) at week 12 • LS mean difference: 0.28 (95% CI, 0.15 to 0.41; *P* < .001) at week 52 Dupilumab 300 mg vs. placebo • LS mean difference: 0.21 (95% CI, 0.11 to 0.31; *P* < .001) at week 2 • LS mean difference: 0.15 (95% CI, 0.04 to 0.27; *P* = .01) at week 12 • LS mean difference: 0.16 (95% CI, 0.03 to 0.28; *P* = 0.02) at week 52 <u>Postbronchodilator FEV-1</u> CRS subgroup Dupilumab 200 mg vs. placebo • LS mean difference: 0.2 (95% CI, 0.09 to 0.30; *P* < .001) at week 2 • LS mean difference: 0.12 (95% CI, 0.01 to 0.23; *P* = .03) at week 12 • LS mean difference: 0.27 (95% CI, 0.15 to 0.39; *P* < .001) at week 52 Dupilumab 300 mg vs. placebo	52 weeks

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• LS mean difference: 0.21 (95% CI, 0.11 to 0.31; *P* < .001) at week 2 • LS mean difference: 0.18 (95% CI, 0.07 to 0.28; *P* < .001) at week 12 • LS mean difference: 0.14 (95% CI, 0.03 to 0.26; *P* = .02) at week 52 <u>SNOT-22</u> • Clinically significant improvement at 52 weeks in dupilumab vs. placebo Dupilumab 200 mg vs. placebo • LS mean difference: −11.88 (95% CI, −17.59 to −6.18; *P* < .001) at week 52 Dupilumab 300 mg vs. placebo • LS mean difference: −10.32 (95% CI, −15.77 to −4.87; *P* < .001) at week 52 <u>ACQ-5</u> • Clinically significant improvement at 52 weeks in dupilumab vs. placebo Dupilumab 200 mg vs. placebo • LS mean difference: −0.60 (95% CI, −0.90 to −0.30; *P* < .001) at week 52 Dupilumab 300 mg vs. placebo • LS mean difference: −0.54 (95% CI, −0.83 to −0.25; *P* < .001) at week 52 <u>AQLQ</u> • Clinically significant improvement at 52 weeks in dupilumab vs. placebo Dupilumab 200 mg vs. placebo • LS mean difference: 0.58 (95% CI, 0.28 to 0.88; *P* < .001) at week 52 Dupilumab 300 mg vs. placebo	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• LS mean difference: 0.57 (95% CI, 0.29 to 0.86; *P* < .001) at week 52 Annualized rate of severe asthma exacerbation • Dupilumab 200 mg: 63% reduction in CRS subgroup (*P* < .001) • Dupilumab 300 mg: 61% reduction in CRS subgroup (*P* < .001)	
Bachert et al., 2019[22] NCT01920893	None assessed	Effect of dupilumab on patient-reported secondary outcomes Inflammatory biomarkers	EQ-5D-VAS Significant improvement in health status in dupilumab group vs. placebo (*P* < .001) SF-36 • Significant improvement in 5 domains (general health, physical functioning, role-physical, social functioning, vitality) and physical component summary in dupilumab group (*P* < .05) • Significant improvement in 2 domains (role-physical, social functioning and physical component summary in placebo group (*P* < .05)	16 weeks
Bachert et al., 2020[21] NCT01920893	None assessed	Effect of dupilumab on patient-reported secondary outcomes	SNOT-22 Dupilumab (n = 30) vs. placebo (n = 30) • LS mean difference: −18.1 (95% CI, −25.6 to −10.6; *P* < .001) • Clinically meaningful improvement: 93.3% vs. 26.7% EQ-5D-VAS • Significantly greater improvement in dupilumab group vs. placebo (*P* = .02) SF-36 Dupilumab (n = 30) vs. placebo (n = 30)	16 weeks

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• Vitality LS mean difference: 5.66 (95% CI, 0.95 to 10.37; *P* = .020) • Mental health LS mean difference: 5.26 (95% CI, 1.69 to 8.82; *P* = .005) • Mental health component summary LS mean difference: 5.45 (95% CI, 1.42 to 9.48; *P* = .009) <u>HRUQ</u> • Employed participants in the dupilumab group had significantly lower adjusted annualized mean number of sick leave days (*P* = .014, RRR: 98%) CRS disease severity VAS Dupilumab (n = 28) vs. placebo (n = 19) • Moderate score at baseline: 31% vs. 36% • Severe score at baseline: 55.2% vs. 52% • Mild score at 16 weeks: 78.6% vs. 15.8% • Moderate score at 16 weeks: 14.3% vs. 42.1% • Severe score at 16 weeks: 7.1% vs. 42.1%	
Bachert et al., 2016[11] NCT01920893	Change in bilateral NPS from baseline to week 16	Change from baseline in Lund-Mackay CT score, percentage of maxillary sinus containing disease, SNOT-22, UPSIT, PNIF, symptoms (nasal congestion or obstruction, rhinorrhea, loss of sense of sell, nocturnal awakenings, symptom severity)	<u>Change in NPS</u> Dupilumab (n = 30) vs. placebo (n = 30) • LS mean difference: −1.6 (95% CI, −2.4 to −0.7; *P* < .001) <u>SNOT-22</u> Dupilumab (n = 30) vs. placebo (n = 30) • LS mean difference: −18.1 (95% CI, −25.6 to −10.6; *P* < .001) <u>Symptom Severity (VAS)</u> Dupilumab (n = 30) vs. placebo (n = 30) • LS mean difference: −2.1 (95% CI, −3.7 to −0.6; *P* = .008) <u>UPSIT</u> Dupilumab (n = 30) vs. placebo (n = 30)	16 weeks

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• LS mean difference: 14.8 (95% CI, 10.9 to 18.7; *P* < .001) <u>FEV-1</u> Dupilumab (n = 30) vs. placebo (n = 30) • LS mean difference: 0.2 (95% CI, −0.02 to 0.5; *P* = .07) <u>FEV-1 percent predicted</u> Dupilumab (n = 30) vs. placebo (n = 30) • LS mean difference: 7.2 (95% CI, 0.4 to 13.9; *P* = .04) <u>ACQ-5</u> Dupilumab (n = 30) vs. placebo (n = 30) • LS mean difference: −1.1 (95% CI, −1.5 to −0.6; *P* < .001) Nasal congestion or obstruction in the morning Dupilumab (n = 30) vs. placebo (n = 30) • LS mean difference: −0.7 (95% CI, −1.1 to −0.3; *P* < .001) Posterior rhinorrhea in the morning Dupilumab (n = 30) vs. placebo (n = 30) • LS mean difference: −0.5 (95% CI, −0.8 to −0.2; *P* = .002 Lund-Mackay Score Dupilumab (n = 30) vs. placebo (n = 30) • LS mean difference: −8.86 (95% CI, −11.1 to −6.6; *P* < .001) Percent of maxillary sinus volume with disease Dupilumab (n = 30) vs. placebo (n = 30) • LS mean difference: −32.2 (95% CI, −43.1 to −21.4; *P* < .001) PNIF Dupilumab (n = 30) vs. placebo (n = 30)	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			• LS mean difference: 33.1 (95% CI, 12.7 to 53.5; *P* = .002)	
Bachert et al., 2017[9] NCT01362244	Number of participants no longer meeting criteria for surgery 4 weeks after final drug dose (based on NPS and nasal polyposis severity VAS scores)	Number of participants meeting criteria for surgery at each time point Change in nasal polyposis severity VAS score at 25 weeks Change in NPS at 25 weeks Individual VAS symptom scores at 25 weeks (rhinorrhea, mucus in the throat, nasal blockage, loss of smell) SNOT-22 EQ-5D PNIF Olfaction (Sniffin' Sticks Screening-12 test) Spirometry (FEV-1, FVC, peak expiratory flow rate) Blood eosinophil counts Pharmacokinetics	Participants no longer meeting criteria for requiring surgery at 25 weeks Mepolizumab (n = 54) vs. placebo (n = 51): • 30% vs. 10% • *P* = .006 Nasal polyposis severity VAS score improvement at 25 weeks Mepolizumab (n = 42) vs. placebo (n = 31) • Treatment difference = −1.8 (95% CI, −2.9 to −0.8; *P* = .001) • Reduction at 9 weeks: OR = 5.6 (95% CI, 1.2 to 26.6; *P* = .31) • Reduction at 25 weeks: OR = 6.6 (95% CI, 1.3 to 24.5; *P* = .025 <u>Symptom reduction</u> Mepolizumab (n = 42) vs. placebo (n = 31) treatment difference • Rhinorrhea: −2.3 (95% CI, −3.4 to −1.2; *P* < .001) • Mucus in the throat: −2.1 (95% CI, −3.2 to −1.0; *P* < .001) • Nasal blockage: −1.8 (95% CI, −2.9 to −0.7; *P* = .002) • Loss of smell: −1.9 (95% CI, −3.4 to −1.2; *P* < .001) <u>Reduction in TPS</u> Mepolizumab (n = 54) vs. placebo (n = 51) • 50% vs. 27% improved by ≥ 1 point in NPS at 25 weeks <u>SNOT-22</u> Mepolizumab (n = 42) vs. Placebo (n = 32) • Treatment difference = −13.2 (95% CI, −22.2 to −4.2; *P* = .005)	25 weeks

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			EQ-5D No significant differences between groups at 25 weeks PNIF Mepolizumab (n = 42) vs. placebo (n = 32) • mean higher in mepolizumab than placebo • Mean difference 26.7 (95% CI, 3.1 to 50.2; *P* = .027) Olfaction • No statistically significant difference between groups Spirometry • No statistically significant difference between groups at week 25	
Han et al., 2020[25] NCT03085797 SYNAPSE	Change from baseline in TPS at 52 weeks Change from baseline in nasal obstruction VAS score during weeks 49 to 52	Time to first nasal surgery until week 52 Proportion of participants requiring SCS until week 52 Change from baseline in mean overall VAS symptoms score during weeks 49 to 52 Change from baseline in mean composite VAS symptoms score during weeks 49 to 52	Change in TPS Mepolizumab (n = 206) vs. placebo (n = 201) • Average ± SD: −0.9 ± 1.90 vs. −0.1 ± 1.46 • Treatment effect: −0.73 (95% CI, −1.11 to −0.34; *P* < .001) • 50% (n = 104) vs. 28% (n = 57) achieved ≥ 1-point improvement at 52 weeks. OR: 2.74 (95% CI, 1.80 to 4.18; *P* < .001) • 36% (n = 74) vs. 13% (n = 26) achieved ≥ 2-point improvement Change in nasal obstruction VAS score Mepolizumab (n = 206) vs. placebo (n = 201) • Average ± SD: −4.2 ± 3.42 vs. −2.5 ± 3.15 • Treatment effect: −3.14 (95% CI, −4.09 to −2.18; *P* < .001) • 71% (n = 146) vs. 50% (n = 100) achieved ≥ 1-point improvement at 52 weeks • 60% (n = 124) vs. 36% (n = 73) achieved ≥ 3-point improvement	52 weeks

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
		Change from baseline in mean loss of sense of smell VAS symptoms score during weeks 49 to 52 Change from baseline in SNOT-22 score at 52 weeks Proportion of participants with a decrease of ≥ 1 points from baseline in NPS at 52 weeks without surgery Number of courses of SCS and antibiotics at 52 weeks Proportion of participants with a decrease of ≥ 8.9 points from baseline in SNOT-22 without surgery Proportion of participants no longer needing surgery at 52 weeks	• 44% (n = 91) vs. 23% (n = 46) achieved ≥ 5-point improvement Proportion of participants having nasal surgery • Mepolizumab 9% (n = 18) vs. placebo 23% (n = 46) • HR: 0.43 (95% CI, 0.25 to 0.76; *P* = .003) • Treatment effect: −0.43 (95% CI, −0.25 to −0.76; *P* = .003) Proportion of participants no longer meeting criteria for surgery Mepolizumab (n = 206) vs. placebo (n = 201) • 72% (n = 149) vs. 51% (n = 103) • OR: 2.46 (95% CI, 1.59 to 3.79; *P* < .001) <u>Change in overall symptom VAS score</u> Mepolizumab (n = 206) vs. placebo (n = 201) • Average ± SD: −4.3 ± 3.43 vs. −2.5 ± 3.08 • Treatment effect: −3.18 (95% CI, −4.10 to −2.26; *P* = .003) <u>Change in composite VAS score</u> Mepolizumab (n = 206) vs. placebo (n = 201) • Average ± SD: −3.8 ± 3.19 vs. −2.2 ± 2.82 • Treatment effect: −2.68 (95% CI, −3.44 to −1.91; *P* = .02) <u>Change in loss of smell VAS symptom score</u> Mepolizumab (n = 206) vs. placebo (n = 201) • Average ± SD: −2.8 ± 3.61 vs. −1.4 ± 2.65 • Treatment effect: −0.37 (95% CI, −0.65 to −0.08; *P* = .02) • Improvements were greater in participants with fewer previous nasal polyp surgeries <u>Change in SNOT-22 score</u>	

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
		Change from baseline in UPSIT score Blood eosinophil counts Change from baseline in loss of smell VAS, based on number of previous surgeries PNIF at 52 weeks Asthma exacerbation rates ACQ-5 at 52 weeks	Mepolizumab (n = 206) vs. placebo (n = 201) • Average ± SD: −29.4 ± 24.67 vs. −15.7 ± 23.93 • Treatment effect: −16.49 (95% CI, −23.57 to −9.42; *P* = .003) • 73% (n = 150) vs. 54% (n = 106) achieved ≥ 8.9-point improvement. OR: 2.44 (95% CI, 1.60 to 3.73; *P* < .001) Proportion of participants requiring SCS • Mepolizumab 25% (n = 52) vs. placebo 37% (n = 74) • OR: 0.58 (95% CI, 0.36 to 0.92; *P* = .02) • Treatment effect: 0.58 (95% CI, 0.36 to 0.92; *P* = .02) • 82 courses of SCS vs. 124 courses Proportion of participants requiring antibiotics • Mepolizumab 41% (n = 84) vs. placebo 50% (n = 100) PNIF • Treatment effect: 23.1 (95% CI, 10.2 to 36.0; *P* < .001) UPSIT • No significant difference between groups Reduction in blood eosinophils • Mepolizumab 81% reduction vs. placebo by 4 weeks (*P* < .001)	
Gevaert et al., 2011[29] CRT110178	Reduction in TPS at 8 weeks after first drug dose	Changes in CT scan scores NPIT Symptom score Blood eosinophil counts Biomarkers of inflammation	<u>Reduction in TPS</u> Mepolizumab (n = 20) vs. placebo (n =10) • 60% vs. 10% • OR: 13.5; *P* = .018 • −1.3 ± 1.72 vs. 0.00 ± 0.94 • Treatment difference: −1.30 ± 1.51 (*P* = .028) CT score improvement • Mepolizumab > 50% vs. < 20% placebo (*P* = .049)	48 weeks

Author, Year Clinical Trial Number Trial Name	Primary Outcome	Secondary Outcomes	Efficacy Outcome	Follow-Up
			Symptom improvement • No significant difference between groups PNIF • No significant difference between groups Blood eosinophil counts • Significant decrease in ECP levels for mepolizumab vs. placebo ($P < .05$) Biomarkers of inflammation • Significant reduction in serum IL-5Rα in mepolizumab vs. placebo ($P < .001$) • Significant reduction in nasal IL-5Rα, IL-6, IL-1β ($P < .05$) in the mepolizumab group • No significant reduction in nasal ECP, IL-5, total IgE	

Abbreviations. AAS: Angioedema Activity Score. AE: adverse event. AE-QoL: Angioedema Quality of Life Questionnaire. AUC: area under the curve. CU-Q2oL: Chronic Urticaria Quality of Life. DLQI: Dermatology Life Quality Index. HRUQ: HealthCare Resource Utilization Questionnaire; ISS7: Weekly Itch Severity Scale. MID: minimally important difference. SAE: serious adverse event. UAS: Urticaria Activity Score. UAS7; Weekly Urticaria Activity Score.

Table B3. Adverse Events and Discontinuation

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
Chronic Spontaneous Urticaria		
Maurer et al., 2011[13]	*Statistical significance testing was not performed between study groups* Overall AEs: • Omalizumab: 81.5% (22 of 27) • Placebo: 86.4% (19 of 22) Drug-related AEs: • Omalizumab: 22.2% • Placebo 22.7% Most common AEs (>5%): • Diarrhea: Omalizumab: 14.8% (4 of 27) Placebo: 9.1% (2 of 22) • Nasopharyngitis: Omalizumab: 33.3% (9 of 27) Placebo: 50% (11 of 22) • Headache: Omalizumab: 37% (10 of 27) Placebo: 27.3% (6 of 22)	Omalizumab: 0 of 22 Placebo: 4.5% (1 of 22) No deaths occurred during this study
Maurer et al., 2013[2] NCT01292473 ASTERIA II	At least 1 AE: • Placebo: 61% (48 of 79) • Omalizumab 75 mg: 59% (45 of 76) • Omalizumab 150 mg: 67% (59 of 88) • Omalizumab 300 mg: 65% (51 of 79) Any SAE: • Placebo: 2 events in 2 participant each pneumonia and hemorrhoids • Omalizumab 75 mg: 1 event in 1 participant, angioedema • Omalizumab 150 mg: 2 events in 1 participant, angioedema and idiopathic urticaria	Placebo: 0 of 79 Omalizumab 75 mg: 4% (3 of 76) Omalizumab 150 mg: 2% (2 of 88) Omalizumab 300 mg: 0 of 79 No deaths occurred during this study

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
	• Omalizumab 300 mg: 5 events in 1 participant, melanoma in situ, nephrolithiasis, idiopathic urticaria, tonsillectomy, and melena Suspected drug-related AE: • Placebo: 4% (3 of 79) • Omalizumab 75 mg: 9% (7 of 76) • Omalizumab 150 mg: 9% (8 of 88) • Omalizumab 300 mg: 9% (7 of 79)	
Kaplan et al., 2013[4] NCT01264939 GLACIAL	Omalizumab % versus placebo % respectively Included AEs below occurred greater in study drug • Abdominal Pain: 3.2 (8 of 252) vs. 2.4 (2 of 83) • Nasopharyngitis: 8.7(22 of 252) vs. 8.4 (7 of 83) • Sinusitis: 7.5 (19 of 252) vs. 6.0 (5 of 83) • URTI: 7.1 (18 of 252) vs. 2.4 (2 of 83) • Headache: 8.7 (22 of 252) vs. 3.6 (3 of 83) • Cough: 4.0 (10 of 252) vs. 3.6 (3 of 83) • GI disorders overall: 15.9 (40 of 252) vs. 14.5 (12 of 83) • General disorders overall: 11.9 (30 of 252) vs. 9.6 (8 of 83) • Infections and infestations overall: 36.9 (93 of 252) vs. 30.1 (35 of 83) • Musculoskeletal and connective tissue disorders overall: 9.5 (24 of 252) vs. 7.2 6 of 83) • Nervous system disorders: 15.5 (39 of 252) vs. 12.0 (10 of 83) • Respiratory, thoracic, and mediastinal disorders overall: 13.9 (35 of 252) vs. 10.8 (9 of 83) • Skin and subcutaneous tissue disorders: 16.7 (42 of 252) vs. 14.5 (12 of 83) Treatment period SAEs, n (%) • Omalizumab: 7 (2.8), cholelithiasis and viral gastroenteritis, retroperitoneal infection, pelvic abscess, lower respiratory tract infection, angioedema, intermittent claudication • Placebo: 3 (3.6), unstable angina, hypersensitivity, hyperglycemia	Omalizumab: 3 (1.2) Placebo: 1 (1.2)

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
Saini et al., 2015[1] NCT01287117 ASTERIA I	Any AE during treatment period, % • Omalizumab 300 mg: 56.8 (46 of 81) • Omalizumab 150 mg: 69.0 (60 of 87) • Omalizumab 75 mg: 58.6 (41 of 70) • Placebo: 51.3 (41 of 80) Any SAE during treatment period, % • Omalizumab 300 mg: 0 • Omalizumab 150 mg: 3.4 (3 of 87) • Omalizumab 75 mg: 2.9 (2 of 70) • Placebo: 5.0 (4 of 80) Any AE suspected to be caused by study drug, % • Omalizumab 300 mg: 17.3 (14 of 81) • Omalizumab 150 mg: 10.3 (9 of 87) • Omalizumab 75 mg: 8.6 (6 of 70) • Placebo: 5.0 (4 of 80)	Omalizumab, % • 300 mg: 1.2 (1 of 81) • 150 mg: 2.3 (2 of 87) • 75 mg: 0 Placebo, %: 2.5 (2 of 80) No deaths occurred during this study
Staubach et al., 2016[3] Staubach et al., 2018[14] NCT01723072 X-ACT	*During treatment weeks 1 through 12* Any AE • Omalizumab: 68.2% (30 of 44) • Placebo: 72.3% (34 of 47) Any SAE • Omalizumab: 9.1% (4 of 44) • Placebo: 4.3% (2 of 47)	Did not specified between discontinuation due to AE vs. other causes
Metz et al., 2017[15] NCT01599637	Overall AEs • Omalizumab: 85% • Placebo: 70% *Most frequently reported AEs, in order of prevalence and similar between groups, were nasopharyngitis, influenza and urticaria*	Omalizumab: 5% (1 of 20) No deaths occurred during this study
Hide et al., 2017[16] NCT02329223	Any AE, % • Omalizumab 300 mg: 54.8 (40 of 73) • Omalizumab 150 mg: 57.7 (41 of 71)	Omalizumab 300 mg: 0 of 73 Omalizumab 150 mg: 1.4 % (1 of 71)

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
POLARIS	• Placebo: 55.4 (41 of 74) Any SAE, % • Omalizumab 300 mg: 4.1 (3 of 73) • Omalizumab 150 mg: 4.2 (3 of 71) • Placebo: 0 Drug-related AE, % • Omalizumab 300 mg: 9.6 (7 of 73) • Omalizumab 150 mg: 8.5 (6 of 71) • Placebo: 12.2 (9 of 74) Most frequent AEs (≥ 2%): omalizumab 300 mg, omalizumab 150 mg, and placebo respectively, % • Nasopharyngitis: 12.3 (9 of 73), 9.9 (7 of 71), 16.2 (12 of 74) • Eczema: 6.8 (5 of 73), 4.2 (3 of 71), 2.7 (2 of 74) • CSU: 4.1 (3 of 73), 1.4 (1 of 71), 1.4 (1 of 74) • Headache: 4.1 (3 of 73), 4.2 (3 of 71), 6.8 (5 of 74) • Pharyngitis: 4.1 (3 of 73), 4.2 (3 of 71), 0 • Urticaria: 2.7 (2 of 73), 5.6 (4 of 71), 2.7 2 of 74) • Dermatitis contact: 1.4 (1 of 73), 0, 4.1 (3 of 74) • URTI: 0, 4.2 (3 of 71), 0	Placebo: 0 of 74 No deaths occurred during this study
Hide et al., 2018[17] NCT02329223 POLARIS	Any AE, % • Omalizumab 300 mg: 54.3 (19 of 35) • Omalizumab 150 mg: 67.6 (23 of 34) • Placebo: 58.3 (21 of 36) Any SAE, % • Omalizumab 300 mg: 0 • Omalizumab 150 mg: 0 • Placebo: 0 Drug-related AE, % • Omalizumab 300 mg: 14.3 (5 of 35) • Omalizumab 150 mg: 11.8 (4 of 34)	Omalizumab 300 mg: 0 Omalizumab 150 mg: 2.9% (1 of 34) Placebo: 0 No deaths occurred during this study

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
	• Placebo: 13.9 (5 of 36) Most frequent AEs (≥ 2%): omalizumab 300 mg, omalizumab 150 mg, and placebo respectively, % • Nasopharyngitis: 17.1 (6 of 35), 17.6 (6 of 34), 19.4 (7 of 36) • Eczema: 11.4 (4 of 35), 8.8 (3 of 34), 2.8 (1 of 36) • Headache: 2.9 (1 of 35), 2.9 1 of 34), 5.6 (2 of 36) • Pharyngitis: 5.7 (2 of 35), 5.9 (2 of 34), 0 • Dermatitis contact: 0, 0, 5.6 (2 of 36) • Acne: 5.7 (2 of 35), 0, 0 • Bronchitis: 5.7 (2 of 35), 0, 0 • Constipation: 0, 5.9 (2 of 34), 0 • Insomnia: 0, 0, 5.6 (2 of 36)	
Eosinophilic Granulomatosis With Polyangiitis		
Wechsler et al[5] NCT02020889	*No significant difference found between groups* Overall AEs, (%) • Mepolizumab: 97 (66 of 68) • Placebo: 94 (64 of 68) Drug-related AEs, (%) • Mepolizumab: 51 (35 of 68) • Placebo: 35 (24 of 68) SAEs, (%) • Mepolizumab: 18 (12 of 68) • Placebo: 26 (18 of 68) Drug-related SAEs, (%) • Mepolizumab: 4 (3 of 68) • Placebo: 4 (3 of 68)	Mepolizumab: 2% (2 of 68) Placebo: 1% (1 of 68) One death occurred in mepolizumab from cardiac arrest, which was not attributed to the study drug per physician

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
Hypereosinophilic Syndrome		
Rothenberg et al., 2008[6] NCT00086658	Pharyngolaryngeal pain (*P* = .03) • Mepolizumab: 2% (1 of 43) • Placebo: 14% (6 of 42) Pain in extremity (*P* = .047) • Mepolizumab: 2% (1 of 43) • Placebo: 12% (5 of 42) No statistical testing performed on drug related adverse events Mepolizumab related adverse events • Any event: 37% (16 of 43) • Arthralgia: 9% (4 of 43) • Fatigue: 9% (4 of 43) • Increased gamma-glutamyltransferase: 5% (2 of 43)	Mepolizumab: 2% (1 of 43) Placebo: 5% (2 of 42)
Roufosse et al., 2020[7] NCT02836496	*No statistical testing performed on adverse events* Events occurring more frequently in mepolizumab group Any on treatment event • Mepolizumab: 89% (48 of 54) • Placebo: 87% (47 of 54) Drug-related event • Mepolizumab: 22% (12 of 54) • Placebo: 13% (7 of 54) Any on-treatment SAE • Mepolizumab: 19% (10 of 54) • Placebo: 15% (8 of 54) Fatal SAEs • Mepolizumab: 2% (1 of 54) • Placebo: 0% (0 of 54)	Mepolizumab: 2% (1 of 54) Placebo: 4% (2 of 54)

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
	Systemic reactions • Mepolizumab: 2% (1 of 54) • Placebo: 0% (0 of 54) Local injection-site reaction • Mepolizumab: 7% (4 of 54) • Placebo: 4% (2 of 54) Pain in extremity • Mepolizumab: 11% (6 of 54) • Placebo: 4% (2 of 54) URTI • Mepolizumab: 15% (8 of 54) • Placebo: 4% (2 of 54) Arrhythmia • Mepolizumab: 2% (1 of 54) • Placebo: 0 of 54 Bundle branch block left • Mepolizumab: 2% (1 of 54) • Placebo: 0 of 54 Palpitations • Mepolizumab: 4% (2 of 54) • Placebo: 0 of 54	
Chronic Rhinosinusitis and Chronic Rhinosinusitis With Nasal Polyps		
Gevaert et al., 2020[24] POLYP 1: NCT03280550 POLYP 2: NCT03280537	AEs considered related to treatment occurring during the study occurred in 6.7% omalizumab-treated and 3.8% placebo-treated patients • Mild to moderate intensity • Occurred within 24 hours of drug administration	POLYP 1 Discontinued from initial stage (n = 5) • Patient decision = 4 • Investigator decision = 1

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
	• No AEs were identified as risks associated specifically with omalizumab	POLYP 2 • Discontinued from initial stage (n = 6) • Patient decision = 6
Pinto et al., 2010 [28] NCT00117611	No AE occurred during the study	Discontinued (n = 0)
Gevaert et al., 2013[23]	95.7% of all participants reported at least 1 AE • AEs were mild • Common cold occurred more often in omalizumab (53.3%) group vs. placebo (0%; *P* = .02) • 1 participant in the placebo group dropped out due to AE (asthma attack) • 1 participant in the omalizumab group had fatal lymphoblastic lymphoma 1 year after trial completion	Overall discontinuation • Omalizumab = 0 • Placebo = 1
Bachert et al., 2019[10] NCT02912468 NCT02898454 LIBERTY NP SINUS-24 LIBERTY NP SINUS-52	• AEs more common in placebo (74%) vs. dupilumab (69%) group • SAE dupilumab vs. placebo: 3% vs. 6% • No death 2 deaths unrelated to study drug • Placebo group: acute myocardial infarction • SINUS-52 dupilumab group: intracranial hemorrhage resulting from a fall Conjunctivitis • Dupilumab vs. Placebo: 1 vs. 7 Treatment-emergent AEs in ≥ 5% participants • Asthma: dupilumab vs. placebo: 7 vs. 20 • Nosebleed: dupilumab vs. placebo: 25 vs. 20 • Headache: dupilumab vs. placebo: 32 vs. 24 • Redness at injection site: dupilumab vs. placebo: 28 vs. 22 • Nasal polyps: dupilumab vs. placebo: 12 vs. 33 • Nasopharyngitis: dupilumab vs. placebo: 55 vs. 41	AEs • Dupilumab: 11 (3%) • Placebo: 15 (5%) Lack of treatment efficacy • Dupilumab: 1 • Placebo: 4 Other reasons • Dupilumab: 5 • Placebo: 8

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
Fujieda et al., 2021[26] NCT02898454 SINUS-52	There were no deaths in this study Any AE • Dupilumab (q 2 weeks): 81.3% • Dupilumab (q 2 weeks then q 4 weeks): 100% • Placebo: 87.5% Nasopharyngitis • Dupilumab (q 2 weeks): 37.5%% • Dupilumab (q 2 weeks then q 4 weeks): 52.9% • Placebo: 31.3% Infections and infestations • Dupilumab (q 2 weeks): 56.3% • Dupilumab (q 2 weeks then q 4 weeks): 82.4% • Placebo: 68.8% Respiratory, thoracic, and mediastinal disorders • Dupilumab (q 2 weeks): 25.0% • Dupilumab (q 2 weeks then q 4 weeks): 35.3% • Placebo: 50.0%	AE • Dupilumab: 0 • Placebo: 3 Reason not given • Dupilumab: 1 • Placebo: 0
Maspero et al., 2020[27] NCT02414854 LIBERTY ASTHMA QUEST	AEs similar across groups • Dupilumab vs. placebo: 81.0% vs. 83.1% • AEs higher in CRS subgroup (83.5% vs. 89.5%) vs. non-CRS subgroup (80.4% vs. 81.4%) Injection site reactions • Dupilumab vs. placebo: 16.8% vs. 7.9% SAEs in CRS subgroup • Dupilumab vs. placebo: 7.2% vs. 12.8% SAEs in non-CRS subgroup • Dupilumab vs. placebo: 8.5% vs. 7.2%	AE • Dupilumab: 51 • Placebo: 24

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
Bachert et al., 2019[22] NCT01920893	No AE data reported	Not reported
Bachert et al., 2020[21] NCT01920893	No AE data reported	Not reported
Bachert et al., 2016[11] NCT01920893	No reported deaths Any AE • Dupilumab vs. placebo: 100% vs. 83.3% Nasopharyngitis • Dupilumab vs. placebo: 47% vs. 33% Injection site reactions • Dupilumab vs. placebo: 40% vs. 7% Headache • Dupilumab vs. placebo: 20% vs. 17% SAEs • Dupilumab vs. placebo: 2 vs. 6 • No SAEs were considered related to the study drug	AE • Dupilumab: 2 • Placebo: 5 Lack of efficacy • Dupilumab: 0 • Placebo: 2
Bachert et al., 2017[9] NCT01362244	AEs were similar between groups Mepolizumab (n = 52) vs. placebo (n = 52) • Headache: 25% vs. 38% • Nasopharyngitis: 19% vs. 23% • Oropharyngeal pain: 11% vs. 8% • Back pain: 9% vs. 0% • Influenza: 8% vs. 4% • Arthralgia: 6% vs. 6% • Fever: 6% vs. 2%	Overall discontinuation: • Mepolizumab, n = 12 • Placebo, n = 19 Discontinued due to lack of efficacy • Mepolizumab, n = 3 • Placebo, n = 11 Discontinued due to lack of protocol deviation • Mepolizumab, n = 5 • Placebo, n = 1

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
		Discontinued due to AEs • Mepolizumab, n = 3 • Placebo, n = 4 Discontinued due to loss to follow-up • Mepolizumab, n = 0 • Placebo, n = 2 Discontinued due to protocol defined stopping • Mepolizumab, n = 0 • Placebo, n = 1 Discontinued due to participant withdrawal • Mepolizumab, n = 1 • Placebo, n = 0
Han et al., 2020[25] NCTT03085797 SYNAPSE	AEs were similar between groups (82% mepolizumab vs. 84% placebo) AEs considered related to study treatment in 15% (n = 30) mepolizumab vs. 9% (n= 19) placebo SAEs occurred in 6% (n = 12) mepolizumab and 6% (n = 13) placebo • No SAEs were considered related to mepolizumab • Placebo: 1 death due to myocardial infarction	Overall discontinuation • Mepolizumab = 8 • Placebo = 7 AE • Mepolizumab = 4 • Placebo = 4 Lack of efficacy • Mepolizumab = 5 • Placebo = 11 Protocol deviation • Mepolizumab = 0 • Placebo = 1 Pregnancy

Author, Year Clinical Trial Number Trial Name	Adverse Events	N (%) Leading to Discontinuation
		• Mepolizumab = 1 • Placebo = 1 Physician decision • Mepolizumab = 1 • Placebo = 2 Patient decision • Mepolizumab = 12 • Placebo = 15
Gevaert et al., 2011[29] CRT110178	No significant difference in AEs between groups One SAE (diverticulitis) was not considered related to the study drug	Rescue operation performed • Mepolizumab = 4 • Placebo = 3 Rescue medication used • Mepolizumab = 5 • Placebo = 3 Accidental medication • Mepolizumab = 1 • Placebo = 1 Did not show up • Mepolizumab = 1 • Placebo = 2

Abbreviations. AE: adverse event; IgE: Immunoglobulin E; SAE: serious adverse event; URTI: upper respiratory tract infection.

Appendix C. Bibliography of Included Studies

- Bachert C, Hellings PW, Mullol J, et al. Dupilumab improves health-related quality of life in patients with chronic rhinosinusitis with nasal polyposis. *Allergy*. 2020;75(1):148-157.
- Bachert C, Hellings PW, Mullol J, et al. Dupilumab improves patient-reported outcomes in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma. *J Allergy Clin Immunol Pract*. 2019;7(7):2447-2449.e2.
- Casale TB, Murphy TR, Holden M, et al. Impact of omalizumab on patient-reported outcomes in chronic idiopathic urticaria: results from a randomized study (XTEND-CIU). *J Allergy Clin Immunol Pract*. 2019;7(7):2487-2490.e1.
- Fujieda S, Matsune S, Takeno S, et al. The effect of dupilumab on intractable chronic rhinosinusitis with nasal polyps in Japan. *Laryngoscope*. 2021;131(6):E1770-E1777.
- Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013;131(1):110-6.e1.
- Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. 2020;146(3):595-605.
- Hide M, Igarashi A, Yagami A, et al. Efficacy and safety of omalizumab for the treatment of refractory chronic spontaneous urticaria in Japanese patients: subgroup analysis of the phase 3 POLARIS study. *Allergol Int*. 2018;67(2):243-252.
- Hide M, Park HS, Igarashi A, et al. Efficacy and safety of omalizumab in Japanese and Korean patients with refractory chronic spontaneous urticaria. *J Dermatol Sci*. 2017;87(1):70-78.
- Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013;132(1):101-9.
- Maspero JF, Katelaris CH, Busse WW, et al. Dupilumab efficacy in uncontrolled, moderate-to-severe asthma with self-reported chronic rhinosinusitis. *J Allergy Clin Immunol Pract*. 2020;8(2):527-539.e9.
- Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128(1):202-209.e5.
- Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013(10);368:924-35.
- Metz M, Staubach P, Bauer A, et al. Clinical efficacy of omalizumab in chronic spontaneous urticaria is associated with a reduction of FcepsilonRI-positive cells in the skin. *Theranostics*. 2017;7(5):1266-1276.
- Pinto JM, Mehta N, DiTineo M, et al. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. *Rhinology*. 2010;48(3):318-24.
- Roufosse F, de Lavareille A, Schandene L, et al. Mepolizumab as a corticosteroid-sparing agent in lymphocytic variant hypereosinophilic syndrome. *J Allergy Clin Immunol*. 2010;126(4):828-835.e3.
- Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Investig Dermatol*. 2015;135(1):67-75.

- Staubach P, Metz M, Chapman-Rothe N, et al. Omalizumab rapidly improves angioedema-related quality of life in adult patients with chronic spontaneous urticaria: X-ACT study data. *Allergy*. 2018;73(3):576-584.
- Staubach P, Metz M, Chapman-Rothe N, et al. Effect of omalizumab on angioedema in H1 -antihistamine-resistant chronic spontaneous urticaria patients: results from X-ACT, a randomized controlled trial. *Allergy*. 2016;71(8):1135-44.
- Steinfeld J, Bradford ES, Brown J, et al. Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. *J Allergy Clin Immunol*. 2019;143(6):2170-2177.

Appendix D. Bibliography of Excluded Studies

Reference	Exclusion Criteria
Bachert C, Zinreich SJ, Hellings PW, et al. Dupilumab reduces opacification across all sinuses and related symptoms in patients with CRSwNP. *Rhinology*. 2020;58(1):10-17.	Outcomes not in scope
Chong LY, Piromchai P, Sharp S, et al. Biologics for chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2021;3(3):CD013513.	Study design not in scope
Desrosiers M, Mannent LP, Amin N, et al. Dupilumab reduces systemic corticosteroid use and sinonasal surgery rate in CRSwNP. *Rhinology*. 2021;59(3):301-311.	Study design not in scope
Hopkins C, Bachert C, Fokkens W, et al. Late breaking abstract: add-on mepolizumab for chronic rhinosinusitis with nasal polyps: SYNAPSE study. *Eur Resp J*. 2020;56:4616.	Publication type not in scope
Howarth P, Chupp G, Nelsen LM, et al. Severe eosinophilic asthma with nasal polyposis: a phenotype for improved sinonasal and asthma outcomes with mepolizumab therapy. *J Allergy Clin Immunol*. 2020;145(6):1713-1715.	Study design not in scope
Laidlaw TM, Bachert C, Amin N, et al. Dupilumab improves upper and lower airway disease control in chronic rhinosinusitis with nasal polyps and asthma. *Ann Allergy Asthma Immunol*. 2021;126(5):584-592.e1.	Study design not in scope
Maurer M, Sofen H, Ortiz B, et al. Positive impact of omalizumab on angioedema and quality of life in patients with refractory chronic idiopathic/spontaneous urticaria: analyses according to the presence or absence of angioedema. *J Eur Acad Dermatol Venereol*. 2017;31(6):1056-1063.	Study design not in scope
Roufosse FE, Kahn JE, Gleich GJ, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol*. 2013;131(2):461-7.e1-5.	Study design not in scope
Sanchez J, Zakzuk J, Cardona R. Evaluation of a guidelines-based approach to the treatment of chronic spontaneous urticaria. *J Allergy Clin Immunol Pract*. 2018;6(1):177-182.e1.	Study design not in scope
Wahba AA, Abdelfattah AM. Anti-immunoglobulin E therapy: is it a valid option for the management of chronic rhinosinusitis with nasal polyposis? *Egypt J Otolaryngol*. 2019;35:269-277.	Outcomes not in scope

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